MedCrave
Step into the World of Research
International Journal of Molecular Biology: Open Access

Review Article

Open Access
CrossMark

Paradigm change in mutagenesis: polymerase tautomeric models for targeted, delayed and untargeted ultraviolet mutagenesis during error prone and SOS replication of double stranded DNA, containing *cis-syn* cyclobutane thymine dimers or thymine in rare tautomeric forms

Abstract

Polymerase-tautomeric models for targeted ultraviolet mutagenesis is developed that are based on the formation of rare tautomeric bases in DNA bases. Five rare tautomeric forms may form for thymine and adenine. These rare tautomeric forms will be stable if corresponding nucleotides are part of cyclobutane pyrimidine dimers or are in small neighbor of the cyclobutane dimers and during DNA synthesis. It is shown that during error-prone or SOS synthesis the modified or specialized DNA polymerases insert canonical bases opposite the *cis-syn* pyrimidine cyclobutane dimers or DNA bases in rare tautomeric forms; the inserted bases are capable of forming hydrogen bonds with bases in the template DNA. Structural analysis indicates that one type of *cis-syn* cyclobutane thymine dimers containing a single tautomeric base (TT^*_1, with the '*' indicating a rare tautomeric base and the subscript referring to the particular conformation) can cause A:T→G:C transition or homologous A:T→T:A transversion. The *cis-syn* cyclobutane thymine dimers containing T^*_4 result in A:T→C:G transversion, while TT^*_5 dimers can cause A:T→C:G transversion or homologous A:T→T:A transversion. Structural analysis indicates that opposite *cis-syn* cyclobutane thymine dimers TT_2^* it is impossible to insert any canonical DNA bases with the template bases with hydrogen bonds formation. *Cis-syn* cyclobutane thymine dimers wherein a thymine is in the rare tautomeric form T_2^* may result in targeted insertions and targeted deletions. Delayed mutations are an important part of radiation-induced genomic instability. Structural analysis of the insertion of the bases showed that opposite rare tautomeric form of thymine T_3^* adenine can be incorporated, but may be inserted any other canonical base so that between them hydrogen bonds are formed. Opposite canonical thymine cytosine can be incorporated only. If in the synthesis of DNA containing the *cis-syn* cyclobutane dimers TT_3^*, involved DNA polymerases with relatively high fidelity of synthesis, mutations not appear. However, if further DNA synthesis will involve DNA polymerases having a low fidelity of synthesis, there may be base substitution mutations after DNA has been damaged. Canonical *cis-syn* cyclobutane thymine dimers TT may result in targeted delayed transversions T-A→G-C only, *cis-syn* cyclobutane thymine dimers TT_3^* may result in targeted delayed transitions T-A→C-G, targeted delayed transversions T-A→G-C and T-A→A-T. Currently, untargeted mutations are studied in the context of radiation-induced bystander effects. Untargeted base substitution mutations are base substitution mutations then one or some nucleotides are inserted in DNA molecule on, so called, undamaged sites of DNA. Thymine in rare tautomeric forms T_1^*, T_4^* and T_5^* may result in untargeted base substitution mutations. Thymine in rare tautomeric forms T_2^* may result in untargeted insertions.

Keywords: UV mutagenesis, radiation induced bystander effects, radiation induced genomic instability, rare tautomeric forms, targeted base substitution mutations, targeted insertions, targeted deletions, untargeted base substitution mutations, untargeted insertions, targeted delayed base substitution mutations, *cis-syn* thymine cyclobutane dimers, error prone replication, SOS replication

Volume 4 Issue 1 - 2019

Helen A Grebneva
Donetsk Physical and Technical Institute NAS of Ukraine, Ukraine

Correspondence: Helen A Grebneva, Donetsk Physical and Technical Institute NAS of Ukraine, Kiev, Ukraine, Email grebneva@gmail.com

Received: December 17, 2018 | **Published:** January 10, 2019

Introduction

Some features of the ultraviolet mutagenesis

Ultraviolet radiation produces cyclobutane pyrimidine dimers under induced by UVB irradiation.[1,2] *Cis-syn* cyclobutane pyrimidine dimers are a large majority of mutations induced by ultraviolet light.[3,4] In cells of *E. coli*, irradiation with a wavelength of 260 nm produces about 40% of thymine dimers, 5%-19% of cytosine dimers and 19%-22% of dimers consisting of cytosine and thymine. For UVC and UVB, the total relative proportion of cyclobutane pyrimidine dimers formed in the thymine-thymine, thymine-cytosine, cytosine-thymine and cytosine-cytosine sites was about 28%, 26%, 16% and 30%,

respectively. However, for UVA, cyclobutane pyrimidine dimers were formed much more frequently in the thymine-thymine sites than at the thymine-cytosine, cytosine-thymine and cytosine-cytosine sites (57% vs. 18, 11 and 14%, respectively).[5] Cyclobutane pyrimidine dimers are effectively removed by excision repair.[6] If not all dimers are moved *cis-syn* cyclobutane thymine dimers may produce mutations.[7] Mutations occur during error-prone and SOS synthesis.[8–11] They cause targeted base substitution mutations[12,13] targeted insertions targeted deletions, targeted complex mutations and targeted delayed mutations.[14–19] Only 5-12 % of *cis-syn* cyclobutane pyrimidine dimers result in mutations.[20] Mutations occur opposite the cyclobutane pyrimidine dimers is termed targeted mutations.[8–11,20,21] Mutations are formed in the vicinity of the damage are termed untargeted mutations.[22] Long-wave ultraviolet UVA light can cause delayed mutations.[23,24] The delayed mutations are usually point mutations, more than half of them are base substitution mutations. As the experiment shows, DNA damage leading to delayed mutations is usually not removed. Delayed mutations can make a significant contribution to genetic diseases.[25,26]

Models of mutagenesis

At present, the conventional paradigm relates the reason of mutations exclusively to sporadic errors of DNA polymerases. It is assumed that the mutations arise because the DNA-polymerase sometimes incorporates non complementary nucleotides opposite the cyclobutane pyrimidine dimers.[27–29] In the articles,[30–32] the authors suggested that mutations induced by ultraviolet light occur only after deamination of the cytosine or 5-methylcytosine within the pyrimidine dimer. Oxidative damage of the bases is considered the cause of mutagenesis under the action of long-wave ultraviolet light (UVA).[29] According to[33] 7,8-dihydro-8-oxoguanine makes an important contribution to the genotoxicity of UVA irradiation of the yeast *Saccharomyces cerevisiae*. Watson and Crick[34] suggested that spontaneous mutations are formed when hydrogen atoms are attached to the bases of DNA, or bases lose hydrogen atoms due to contact with water molecules; which influences the character of base pairing. The participation of rare tautomeric forms in mutagenesis was repeatedly discussed.[35–38] A large number of works devoted to the study of rare tautomeric forms have been performed, both in DNA bases and in model molecules.[39] It was shown that after cytosine was irradiated with UV light (cytosine was isolated in a low-temperature argon matrix), it changed from the main tautomeric form to rare tautomeric forms, their ratio depended on the intensity of irradiation.[40] In Ref[39] the nature of the defect states in crystals of bases of nucleic acids irradiated with UV light by the method of thermally stimulated luminescence was studied. It was concluded that there are rare tautomeric forms of cytosine in the investigated crystals[39] However, all currently existing mutagenesis models cannot explain most of the phenomena of mutagenesis.[41,42] Polymerase paradigm.[27–29] tautomer model by Watson and Crick[34–37] and deamination model[30–32] claim an explanation targeted base substitution mutations only. Cyclobutane pyrimidine dimer consisting deamination cytosine or 5-methylcytosine[30–43] may result in base substitution mutations. Some data implicate the deamination of cytosine to uracil as a possible cause, but other results appear to indicate that the rate of deamination is too low (in the range of 10^{-10}sec^{-1} by *in vitro* measurement) for this to be significant in *Escherichia coli*.[44] The experimental data on the incorporation of DNA bases by various DNA polymerases were summarized and called A-rule.[28] It turned out that opposite the *cis-syn* cyclobutane thymine dimers DNA polymerase inserted adenine most often[44] but sometimes they inserted guanine, thymine or cytosine.[45–48] In the polymerase paradigm, it is assumed that both matrix and inserted bases are in canonical tautomeric forms. We make a structural analysis of the inserting of the canonical bases found in the study of A-rule in the papers opposite *cis-syn* cyclobutane thymine dimers or (6-4) adducts.[49–50] The canonical tautomer of guanine (Figure 1) and the canonical tautomer of thymine (Figure 1c) cannot form hydrogen bonds with canonical tautomers of thymine for steric reasons. But canonical tautomeric forms of cytosine can be incorporated opposite the canonical tautomer of thymine (Figure 1b). Specialized and modified DNA polymerases incorporates canonical bases capable of forming hydrogen bonds with *cis-syn* cyclobutane pyrimidine dimers in template DNA.[51–62] Therefore, the polymerase paradigm cannot explain the mechanism for the formation of targeted base substitution mutations (for a more detailed analysis see in[50] In my opinion, now mutagenesis as an area of research is in deep crisis.

The idea of Watson and Crick that rare tautomeric forms of DNA bases can play an important role in mutagenesis[34] is certainly magnificent, but requires further development. To understand the mechanisms of the formation of different mutations under the action of different mutagens, it is necessary to understand what happens when at least one mutagen acts. As such a model, in my opinion, ultraviolet mutagenesis is best suited. I believe that in order to understand how mutations are formed under the action of ultraviolet light, the following should be done. It is necessary to study the processes that occur when an ultraviolet quantum of energy interacts with a DNA molecule. It is necessary to see to what chemical changes of DNA structure this can lead. It is necessary to study the conditions under which these chemical changes will be stable. It is necessary to study what mutations they can lead to in the case of error prone or SOS replication of DNA that has such damage. This plan was implemented in several article cycles.[63–87] A semiempirical potential function capable of describing hydrogen bonds with lengths different from equilibrium has been developed[63,64] It was used to find potential curves of the guanine-cytosine pair for several lengths of hydrogen bonds.[63,65] The obtained curves were used to study the nature of the vibrations of atoms and atomic groups for isolated bases and guanine-cytosine base pair for hydrogen bonds in the ground and excited states.[63,65,66] The problem was solved for an isolated guanine-cytosine pair[63,65] and a pair of guanine-cytosine located in the DNA strand.[63,66] The theory of heat deexcitation of hydrogen bond protons in paired bases of DNA molecules was developed.[63,67] The previously obtained results[63,67] made it possible to estimate the lifetime of the excited hydrogen bond with respect to thermal transitions. The processes of propagation of excitation energy along the DNA molecule were studied, a new quasiparticle, a proton exciton, was predicted, and its properties were studied.[68] It turned out that the main contribution to the process of hot and cold spots of ultraviolet mutagenesis formation is made by the processes of propagation of excitation energy along the DNA molecule.[69] All these results were used in the construction of a model for rare tautomeric forms of DNA bases formation upon irradiation of a DNA molecule with ultraviolet light.[63,75] The rare tautomeric forms are stable when the respective bases are involved in cyclobutane thymine dimers. This is because the DNA strand bends once pyrimidine dimers arise, and the hydrogen bonds between the bases are broken between the bases that neighbor the cyclobutane pyrimidine dimers.[88,89] The rare tautomeric forms of DNA bases are stable in DNA synthesis.[76] These conclusions were confirmed by experiments.[61,62] The results of studies on the structure of the active

centers polymerases show that the bases in rare tautomeric forms may exist in the active sites of DNA polymerases.[61,62] These results served as the basis for the development of the polymerase-tautomeric models for targeted ultraviolet mutagenesis,[41,42,50,63,69,70,72,73,75,76,78–82] radiation-induced bystander effects[71,74,77,84,85] and radiation-induced genomic instability.[49,63,83,86] The polymerase-tautomeric models are based on Watson and Crick's hypothesis that the mutagenesis is based on the ability of the bases to change the tautomeric state. I propose the mechanisms of targeted base substitution mutations formation during error-prone or SOS synthesis of DNA containing *cis-syn* cyclobutane cytosine and thymine dimers.[41,42,75] I propose the mechanisms of targeted insertions formation during error-prone or SOS synthesis of DNA containing *cis-syn* cyclobutane cytosine[78] and thymine dimers.[42,79] A mechanisms was proposed for targeted complex insertions[42,81] and targeted deletions[42,80] caused by *cis-syn* cyclobutane thymine dimers.

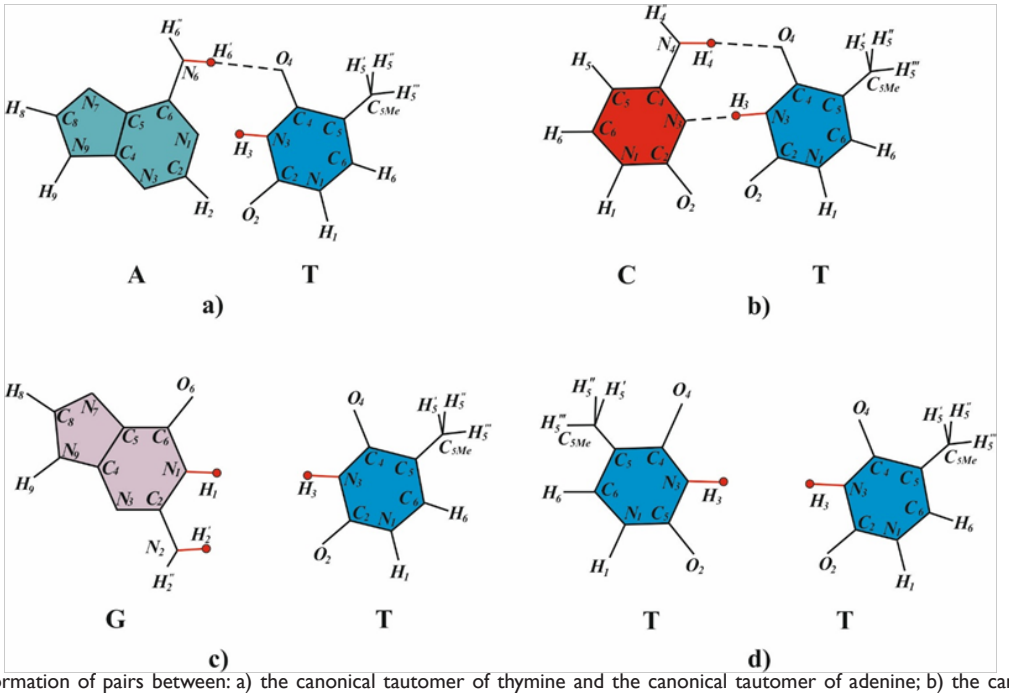

Figure 1 Possible formation of pairs between: a) the canonical tautomer of thymine and the canonical tautomer of adenine; b) the canonical tautomer of thymine and the canonical tautomer of cytosine; c) the canonical tautomer of thymine and the canonical tautomer of guanine; d) the canonical tautomer of thymine and the canonical tautomer of thymine.[49]

The mechanism of rare tautomeric forms formation in DNA base pairs

A mechanism for changes in the tautomeric state of base pairs has been propose.[90] The destiny of DNA-absorbed UV-quantum significantly depends on several factors. On the one hand, it depends on nucleotide composition of the neighboring pairs of bases and, on the other hand, on the relation between the lowest singlet (short-lived) and triplet (long-lived) levels of energy of various bases.[75] It has been shown, that the tautomeric changes can occur at no radiative de excitation of the DNA, which has absorbed the UV-quantum from triplet levels of energy owing to strong forced oscillations. Such oscillations result in changes of lengths of hydrogen bonds. The hydrogen bonds that are formed between the DNA bases are characterized by a strong valence bond with one of the partner atoms in the H-bond, and a weak bond with the other. When the H-bond length changes, the length of a valence bond changes very little. The distance from the hydrogen to the second atom, however, varies considerably. When the hydrogen bond becomes shorter, atom of hydrogen is almost in the center of hydrogen bond. When the H-bond is extended, the hydrogen atom can assume new position.

It was assumed that the tautomeric state of the constituent bases may change during the formation of cyclobutane pyrimidine dimers.[75] A mechanism for changes in the tautomeric state of base pairs has been proposed for the case when DNA is UV-irradiated and cyclobutane pyrimidine dimers are formed.[75] The rare tautomeric forms of bases are stable at *cis-syn* cyclobutane pyrimidine dimers formation and in DNA synthesis.[90] The forms are stable when the respective bases are involved in cyclobutane thymine dimers.[75] The rare tautomeric forms of bases are stable because, at *cis-syn* cyclobutane pyrimidine dimers formation, the DNA strand is bent and the hydrogen bonds between the bases are significantly weakened or are broken.[88,89] When the hydrogen bond becomes weaker it becomes longer. As shown in[91] in this case, there is a second minimum. To find out what new tautomeric forms of DNA bases can be formed, I used the structural - dynamic model of semi-open states of the DNA by Hovorun.[92] Five new rare tautomeric conformations of adenine and thymine base pairs (Figure 2)[75] and seven new rare tautomeric conformations of G:C base pairs are proposed that are capable of influencing the character of base pairing.[41] It is well known that the A:T base pair contains two hydrogen bonds (Figure 2a). Hovorun[92] assumes that it is possible to have a metastable state having a third hydrogen bond. Rare tautomeric forms of thymine T^*_4 (Figure 2e) and T^*_5 (Figure 2f) are possible only in the case when such short-lived semi-open states are formed. It is easy to see that the mechanism of formation of rare tautomeric forms of paired bases of DNA depends only on the properties of hydrogen bonds and properties of DNA molecules. Consequently, it will be true under the action of a DNA molecule of any mutagens. Since

the mutagen causes any damage to the DNA molecule, it exhibits excitation energy. This energy is absorbed by one of the DNA bases this lead to the excitation of the electron-vibrational states. At the thermal relaxation of the excitation energy it will cause fluctuations in the lengths of the hydrogen bonds between paired bases. Change in lengths of the hydrogen bonds can lead to changes of tautomeric states of DNA bases. Under certain conditions, the formed rare tautomeric forms of DNA bases will be stable.

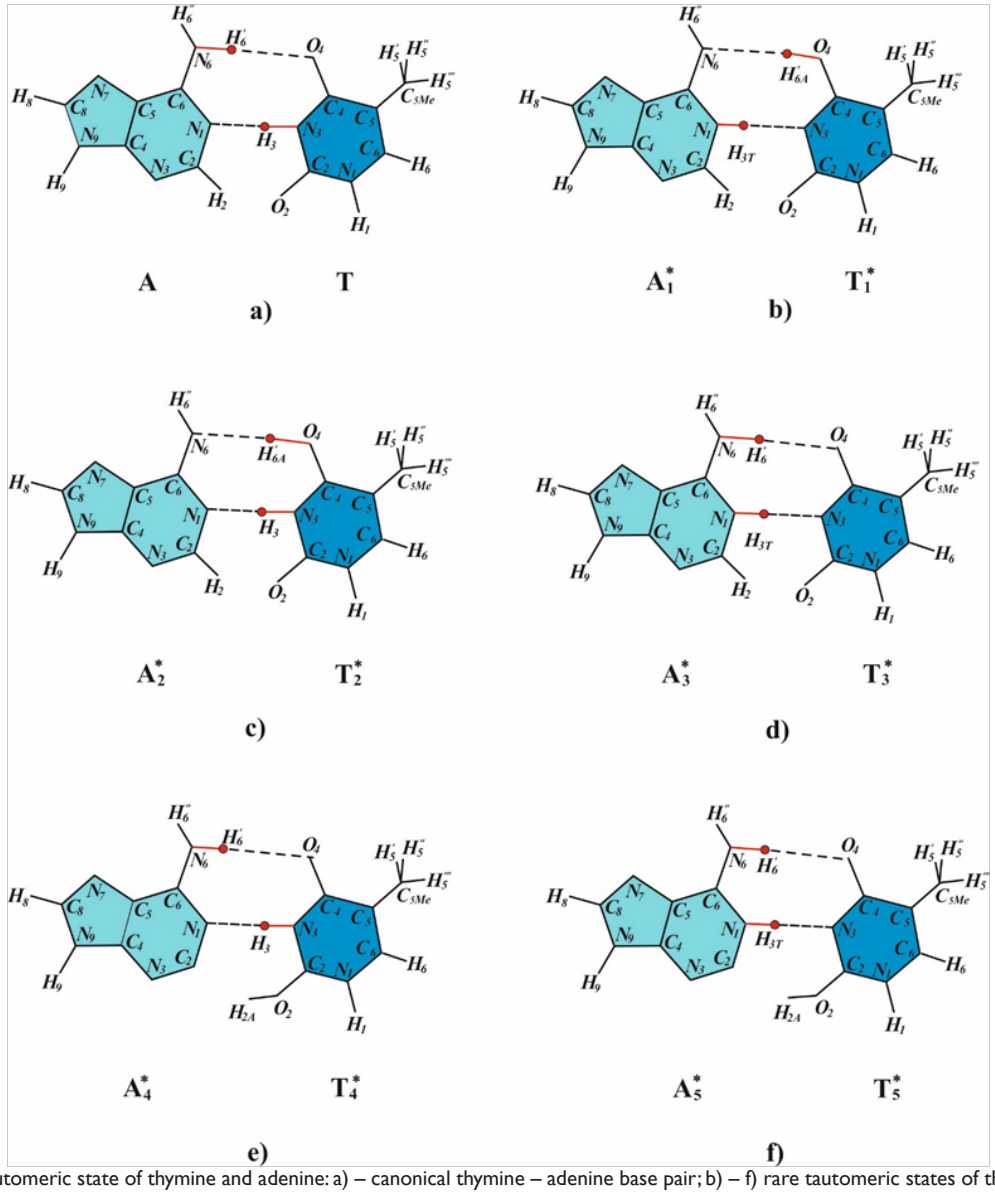

Figure 2 Possible tautomeric state of thymine and adenine: a) – canonical thymine – adenine base pair; b) – f) rare tautomeric states of thymine and adenine.[73]

Polymerase tautomeric models for targeted base substitution mutagenesis during error prone and SOS synthesis of double stranded DNA, containing cis-syn cyclobutane thymine dimers

SOS induction allows DNA synthesis to occur even on templates containing the dimers[94] replication on a damaged DNA template, however, results in mutations.[93,94] Numerous experimental data[61,62] support conclusion that during the error-prone or SOS synthesis or a "sliding clamp" involved in the synthesis[95–102] the canonical bases, which can form hydrogen bonds with bases of the template DNA, are incorporated opposite cyclobutane pyrimidine dimers.[76] Thus, the following conclusions can be drawn. An exonuclease-free DNA polymerase or a DNA polymerase with the 3′→5-exonuclease activity suppressed by the sliding clamp can incorporate bases opposite DNA bases that are in rare tautomeric forms. Such bases can form hydrogen bonds with the bases of the template DNA, and canonical bases are, as a rule, incorporated. Based on these conclusions, let us now consider the mechanisms for the formation of targeted transitions and transversions during the SOS-replication of double-stranded DNA containing *cis-syn* cyclobutane thymine dimers. Cyclobutane pyrimidine dimers and (6-4) adducts cause substutution mutations.[20,21,103] Experimental data on the operation of a large number of polymerases which incorporate the bases opposite abasic sites, cyclobutane pyrimidine dimers and (6-4) photoproducts have been analyzed, such polymerases as iota (ι), kappa (κ), T7, Dpo4, polξ, DinB family, Rew I, polV, polIV, polα, Tag(pol I family), HIV reverse transcriptase, polδ have been analyzed in Ref[28] The following analysis indicates how DNA containing dimers

with one or two bases in the rare tautomeric forms shown in Fig. 2 are replicated during error-prone or SOS synthesis. Canonical tautomeric forms of guanine can be incorporated opposite T^*_1 (Figure 3a). In this case, A:T→G:C transition will result. The insertion of a canonical tautomeric form of thymine opposite T^*_1 (Figure 3b) produces homologous A:T→T:A transversion. The rare T^*_1 tautomer cannot form hydrogen bonds with canonical tautomers of cytosine or adenine for steric reasons. The rare T^*_4 thymine tautomer is capable of forming three hydrogen bonds with cytosine (Figure 3e). This pairing results in A:T→C:G transversion. T^*_5 can form two hydrogen bonds with cytosine (Figure 3c) and two hydrogen bonds with thymine (Figure 3d). These pairings result in homologous A:T→T:A transversion and in A:T→C:G transversion, respectively.[72,77] Nevertheless, polymerases do incorporate mismatched nucleotide base pairs at low frequency.[104] Recently, a T•G mismatch has been observed to adopt a canonical base-pair structure in a polymerase, due to an ionization event, demonstrating that noncanonical hydrogen-bonding pattern can arise in a polymerase.[61] The results[61] suggest a catalytic mechanism for misinsertion and mismatch extension that is in common with correct incorporation, and they support Watson and Crick's original idea that spontaneous base substitutions, in this case A•T to G•C transition mutations, may result from mismatches shaped like correct base pairs. Wang et al.[62] shown that under conditions which stabilize an enzyme conformation that places a nucleotide at the site of incorporation, the C•A mismatch adopts a tautomeric cognate base-pair shape.

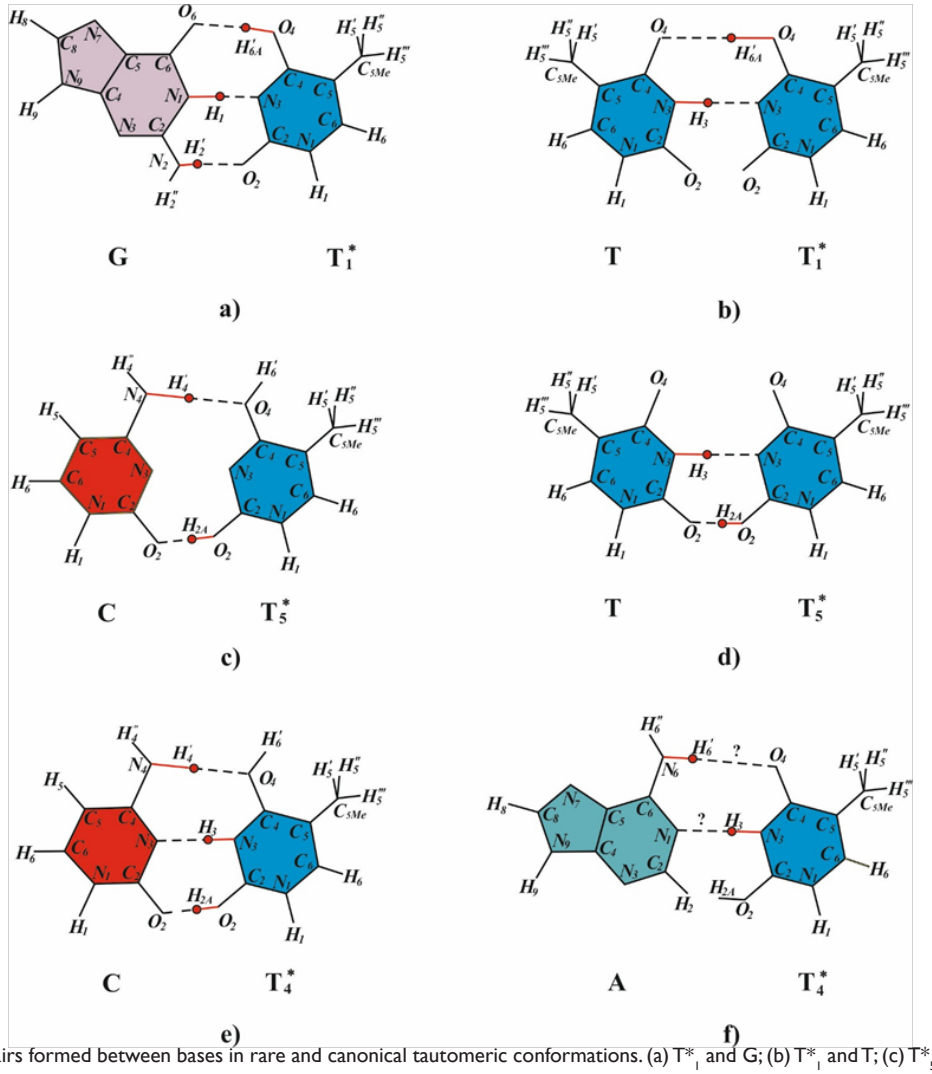

Figure 3 Possible base pairs formed between bases in rare and canonical tautomeric conformations. (a) T^*_1 and G; (b) T^*_1 and T; (c) T^*_5 and C; (d) T^*_5 and T; (e) T^*_4 and C; (f) T^*_4 and A.[72]

Polymerase tautomeric models for targeted insertional mutagenesis during error prone and SOS synthesis of double stranded DNA, containing cis-syn cyclobutane thymine dimers

Insertions are the structural DNA changes wherein one DNA strand becomes longer than the other as a result of an insertion of a number of nucleotides.[105] Insertions may be targeted and untargeted types.[106] Frameshifts mutations often account for approximately one-third of all mutations.[107] Frameshift mutations most commonly arise in DNA sites with a homogenous nucleotide composition, such as monotonous runs of G-C or A-T pairs or sequences with alternating A-T and T-A pairs. Now it is still unclear how frameshift mutations arise at cyclobutane pyrimidine dimers. The Streisinger model[108] is now the best-grounded model of frameshift mutations.[109–111] suggesting gaps and DNA strand slippage during synthesis as the causes of mutations. Consider the formation of longer insertions. A DNA site is assumed to have a homogenous nucleotide composition and carry two *cis-syn* cyclobutane pyrimidine dimers in one strand. One dimer is the *cis-syn* cyclobutane thymine dimer TT_2*, and the other is a cyclobutane

pyrimidine dimer whose bases occur in the canonical tautomeric forms (Figure 4) (Figure 5a). A structural analysis is performed for the incorporation of DNA nucleotides opposite to T_2* (Figure 4) to identify the canonical nucleotides that can be added opposite to T_2* to allow hydrogen bonding of the two bases. Canonical thymine cannot be added opposite to T_2* by DNA polymerase because of repulsion between the hydrogen H_3 of the canonical thymine and H_3 of T_2* (Figure 4c). Adenine cannot be added because of repulsion between H'_6 of adenine and H'_{6A} of T_2* (Figure 4d). Cytosine incorporation is prevented by repulsion between H_4' of cytosine and H'_{6A} of T_2* (Figure 4e), and guanine incorporation is prevented by repulsion between H'_1 of guanine and H_3 of T_2* (Figure 4f). That is, none of the canonical bases can be incorporated opposite to T_2*.[79] A one-nucleotide gap arises opposite to a *cis-syn* cyclobutane dimer TT_2* (Figure 5b) as a result of translesion synthesis driven by modified *E.coli* DNA polymerase III or mammalian DNA polymerase δ or ε or specialized (mammalian Polη or Polζ or *E.coli* DNA polymerase IV or V) DNA polymerases. As was demonstrated experimentally, such a gap arises during DNA synthesis when the template contains an abasic site, leading to a one-nucleotide deletion.[112] The nascent DNA strand may slip (Figure 5c) because a bend forms in the site containing cyclobutane pyrimidine dimers and the hydrogen bonds are disrupted.[113-116] Since the template in question has a homogenous nucleotide composition, the growing DNA strand may form a small loop (Figure 5d) via pairing with the adjacent nucleotide of the opposite strand. The growing strand is extended by only one nucleotide in this case. The gap increases to two nucleotides; and when it is filled in by constitutive DNA polymerases, a targeted one-nucleotide insertion arises (Figure 5e).[79] Specialized or modified DNA polymerases drive DNA synthesis. Hence, a one-nucleotide gap arises opposite to the *cis-syn* cyclobutane thymine dimer TT_2*. The gap arises opposite to T_2*. The end of the DNA strand may slip, especially when another (any) cyclobutane dimer occurs in the vicinity of the dimer TT_2* because the strand bends and hydrogen bonds are disrupted opposite to such dimers. Since the template region is structurally homogeneous, the end of the growing strand may form hydrogen bonds with a neighbor region to produce a large loop. The resulting large gap is usually filled in by constitutive DNA polymerases, leading to insertion of several nucleotides. A targeted insertion forms in this case. The above mechanisms of insertions agree with the Streisinger model.[108]

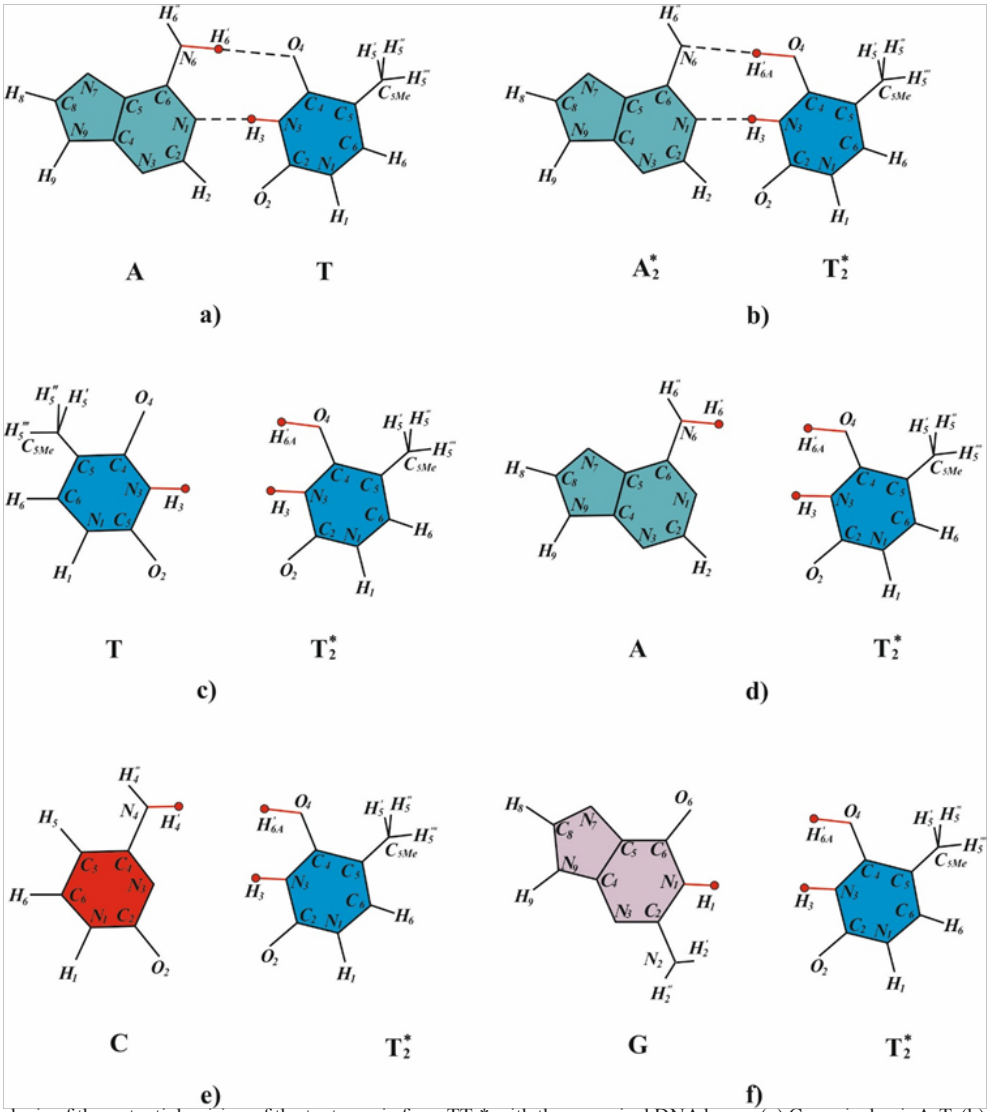

Figure 4 Structural analysis of the potential pairing of the tautomeric form TT_2* with the canonical DNA bases. (a) Canonical pair A-T. (b) Pair A_2*-T_2*, wherein the bases are in the rare tautomeric state. The possibility of T_2* pairing is structurally analyzed for the canonical DNA bases (c) thymine, (d) adenine, (e) cytosine, and (f) guanine.[79]

Citation: Grebneva HA. Paradigm change in mutagenesis: polymerase tautomeric models for targeted, delayed and untargeted ultraviolet mutagenesis during error prone and SOS replication of double stranded DNA, containing *cis-syn* cyclobutane thymine dimers or thymine in rare tautomeric forms. *Int J Mol Biol Open Access.* 2019;4(1):1–15. DOI: 10.15406/ijmboa.2019.04.00091

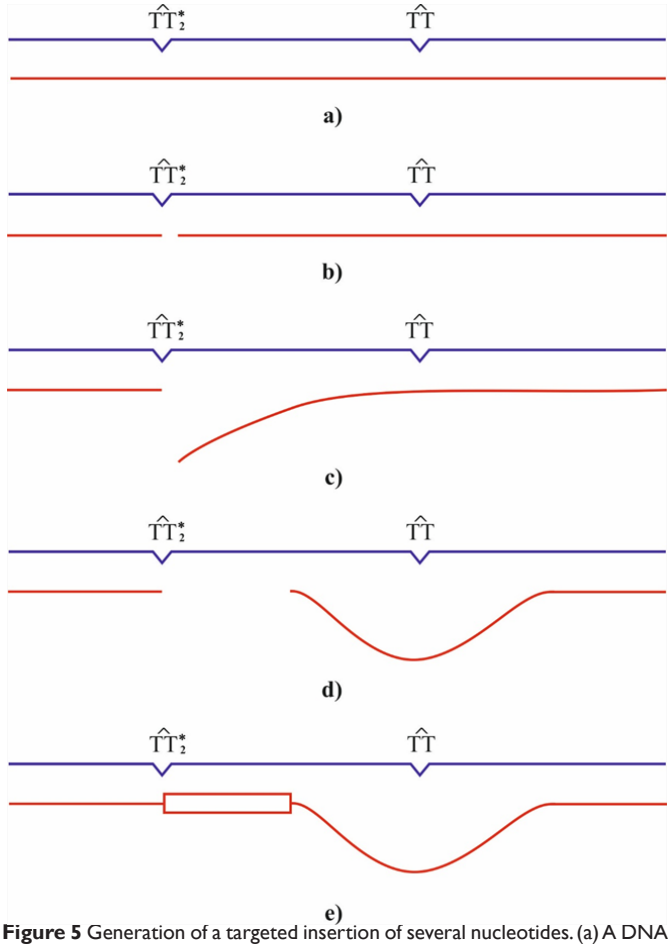

Figure 5 Generation of a targeted insertion of several nucleotides. (a) A DNA site contains the *cis-syn* cyclobutane dimers TT_2^* and TT. (b) A one-nucleotide gap arises opposite to the cyclobutane dimer TT_2^*. (c) The end of the growing DNA strand slips, and (d) a loop forms. (e) The large gap is filled in to produce a targeted insertion of several nucleotides.[79]

Polymerase tautomeric models for targeted deletional mutagenesis during error prone and SOS synthesis of double stranded DNA, containing cis-syn cyclobutane thymine dimers

The polymerase tautomeric model for targeted deletions (frameshift mutations) caused by *cis-syn* cyclobutane thymine dimers.[80] A one-nucleotide gap arises opposite to a *cis-syn* cyclobutane dimer TT_2^* (Figure 6b) as a result of translesion synthesis driven by modified or specialized DNA polymerases. As was demonstrated experimentally, such a gap arises during DNA synthesis when the template contains an abasic site, leading to a one-nucleotide deletion.[112] The site in nascent DNA strand may be lost (Figure 6c) because a bend forms in the site containing cyclobutane pyrimidine dimers and the hydrogen bonds between the bases are broken.[88, 89, 113–116] A DNA site containing the *cis-syn* cyclobutane dimers TT_2^*, may form a loop as shown in (Figure 6e). The resulting smaller gap is usually filled in by constitutive DNA polymerases (Figure 6f), leading to the precipitation of several bases (deletion formation).[80] One nucleotide deletions appear most often. In this case, one nucleotide falls. This deletion may cause a one *cis-syn* cyclobutane dimer TT_2^*.[80] The mechanisms of deletions agree with the Streisinger model.[108]

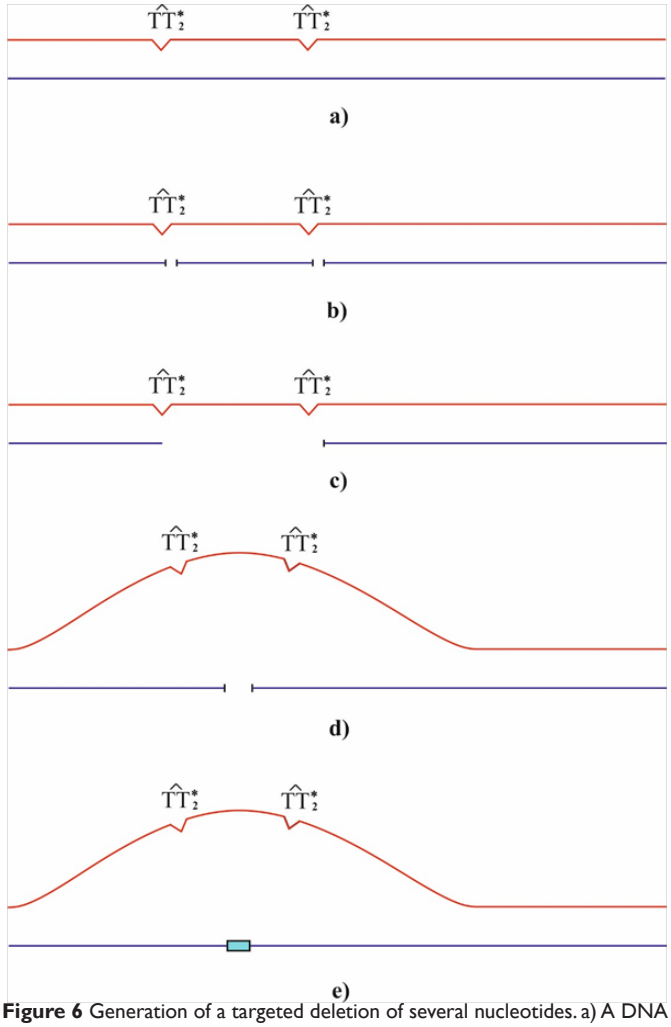

Figure 6 Generation of a targeted deletion of several nucleotides. a) A DNA site contains the *cis-syn* cyclobutane thymine dimers TT_2^*; b) a post replicative gap arises opposite to *cis-syn* cyclobutane dimers TT_2^*; c) post replicative gap is filled using modified or specialized DNA polymerases. One-nucleotide gaps arise opposite to the *cis-syn* cyclobutane thymine dimers TT_2^*; d) site of the DNA strand is lost; e) a loop forms; f) the gap is filled. An insertion of several nucleotides formed, but smaller than the fallen DNA site. A targeted deletion of several nucleotides is formed.[80]

Polymerase tautomeric models for targeted complex insertions during error prone and SOS synthesis of double stranded DNA, containing cis-syn cyclobutane thymine dimers

Complex mutations are frameshift mutations with an adjacent base substitution.[117–119] A polymerase-tautomeric model for targeted complex insertions caused by the *cis-syn* cyclobutane thymine dimers were suggested.[42,81] *Cis-syn* cyclobutane dimers TT_2^* may result in targeted insertion.[42,79] A one-nucleotide gap forms opposite *cis-syn* cyclobutane dimers TT_2^* (Figure 7b). The nascent DNA strand may slip because a bend forms and the hydrogen bonds between the bases are broken[88, 89,113–116] (Figure 7c). Since the template site is structurally homogeneous, the end of the growing strand may form hydrogen bonds with a neighbor site to produce a large loop (Figure 7d). The resulting large gap is usually filled in by constitutive DNA polymerases (Figure 7e), leading to targeted insertion of several nucleotides. Four

nucleotides will be incorporated. One nucleotide will be incorporated opposite thymine T_2*. But a one-nucleotide gap was opposite *cis-syn* cyclobutane dimers TT_2* (Figure 7b). Consequently, an additional three nucleotides incorporated, the insertion of three nucleotides is formed. A DNA site containing the *cis-syn* cyclobutane thymine dimers TT_5*, TT_2*, TT_1* and TT_5* where the thymine molecules in the rare tautomeric forms, corresponding to (Figure 2). They are in one of DNA strands. The opposite DNA strand containing the molecules of adenine A^*_5, A^*_2, A^*_1, and A^*_5, in the rare tautomeric forms and conforming (Figure 2). A one-nucleotide gap arises opposite the *cis-syn* cyclobutane thymine dimers TT_2* (Figure 7b). Thymine or guanine is inserted opposite T_5* in first *cis-syn* cyclobutane thymine dimers TT_5*. Guanine or thymine is inserted opposite T_1*. Cytosine or thymine is inserted opposite T_5* in second *cis-syn* cyclobutane thymine dimers TT_5* (Figure 7b). The end of the growing DNA strand slips (Figure 7c). d) A loop forms (Figure 7d). The large gap is filled in to produce a targeted insertion of several nucleotides (Figure 7e). The DNA site ATTGTTTTTTTTTATTGT consisting 18 nucleotides has been replaced by the DNA site ATA(G)GTTTTTTTTTTC(A)TATG(A)GT consisting 21 nucleotides (Figure 7f). Thus, the DNA site ATTGTTTTTTTTTATTGT consisting of 18 nucleotides is replaced by DNA site ATA(G)GTTTTTTTTTTC(A)TATG(A)GT consisting of 21 nucleotides. The same *cis-syn* cyclobutane thymine dimers can lead to several targeted base substitution mutations.[76] For this reason, different targeted complex mutations may appear on the same site of DNA. The DNA site ATTGTTTTTTTTTATTGT consisting of 18 nucleotides may be replaced by 8 DNA site consisting of 21 nucleotides. There are ATAGTTTTTTTTTTCTATGGT, or ATAGTTTTTTTTTTATATGGT, or ATAGTTTTTTTTTTCTATAGT, or ATAGTTTTTTTTTTATATAGT, or ATGGTTTTTTTTTTCTATGGT, or ATGGTTTTTTTTTTATATGGT, or ATGGTTTTTTTTTTCTATAGT, or ATGGTTTTTTTTTTATATAGT DNA sites.[42,81]

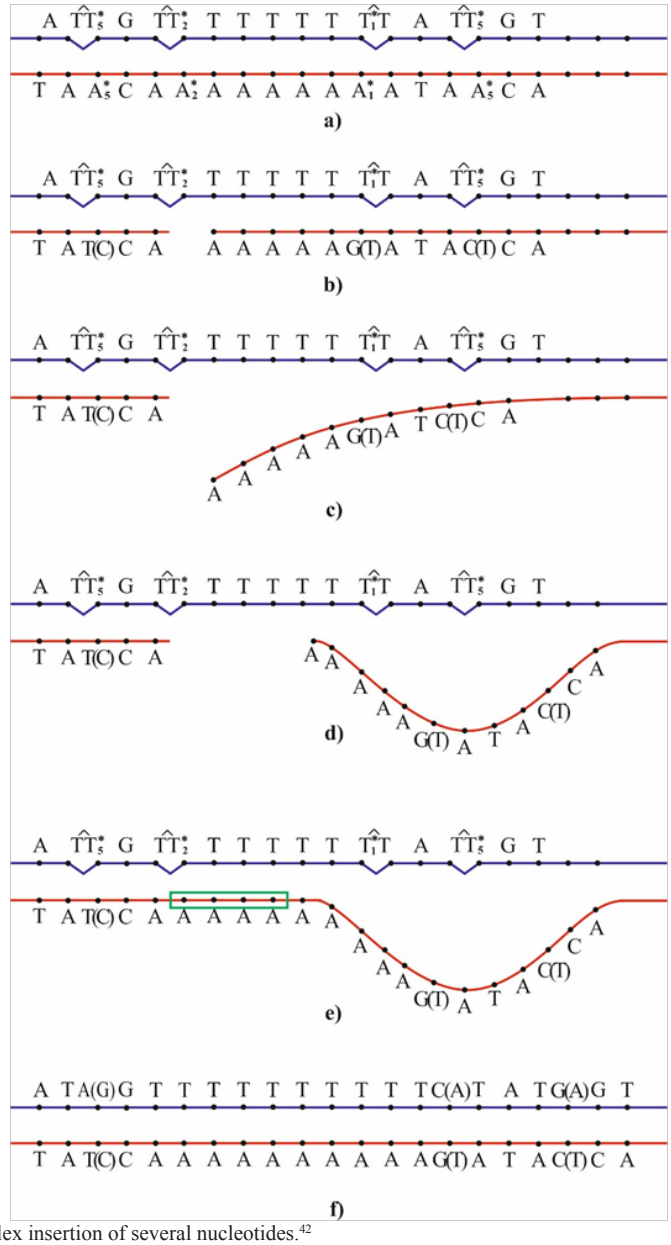

Figure 7 Generation of a targeted complex insertion of several nucleotides.[42]

Polymerase tautomeric models for radiation induced genomic instability: targeted delayed base substitution mutations during error prone and SOS synthesis of double stranded DNA, containing cis-syn cyclobutane thymine dimers

The conventional view of radiation mutagenesis is that radiation induces most mutations in cells shortly after irradiation.[120] Delayed mutations are mutations occur in the progeny of the irradiated cell after many generations of cell division.[18] Ultraviolet light induces delayed mutations.[23] The delayed mutations are usually point mutations.[121] The genome instability results in base substitutions or deletions or insertions of a few nucleotides. Radiation-induced genome instability is a critical early event in the multi-step sequence leading to radiation-induced cancer.[122] Radiation-induced genome instability is the process whereby gene mutations increases.[18,123,124] Delayed effects include hyper mutation, hyper-homologous recombination, chromosome instability and reduced clonogenic survival (delayed death).[125] Delayed mutations and untargeted mutations are two features of genomic instability.[126] Although radiation-induced genomic instability has been studied for years, questions regarding the time course of formation and mechanism of induction of delayed mutations remain to be answered.[18,127,128] I proposed polymerase-tautomeric models for radiation induced genomic instability: targeted delayed base substitution mutations during error prone and SOS synthesis of double-stranded DNA, containing *cis-syn* cyclobutane cytosine[86] and thymine[49,83] dimers. In order to determine which of the canonical bases will be inserted by the SOS-modified DNA-polymerase opposite *cis-syn* TT_3* cyclobutane thymine dimers (Figure 8), consider the constraints on the formation of hydrogen bonds between the bases of the template DNA and the inserted bases. During SOS synthesis of DNA containing dimers, nucleotide bases are inserted opposite the dimers without the removal of the dimer-containing sites. This is only possible when the DNA-polymerase is pressed on the DNA by the "sliding clamp", obstructing the operation of exonucleases, or when the synthesis involves specialized DNA polymerases, such as *E. coli* polymerase V or IV, or when the specialized DNA-polymerase is pressed on the DNA by the "sliding clamp". The rare T_3* thymine tautomer is capable of forming one H-bond with canonical adenine (Figure 8c). But T_3* can form two H-bonds with canonical guanine (Figure 8d) and one H-bond with canonical cytosine (Figure 8e) and one H-bond with canonical thymine (Figure 8f). Consider a DNA site with a *cis-syn* TT_3* cyclobutane thymine dimers. Let other *cis-syn* cyclobutane pyrimidine dimers are located quite far from it. Since the damage is only one, the synthesis through the damage will go quite quickly and with high accuracy. For example, the synthesis will be carried out using Pol III DNA polymerase of *Escherichia coli* or eukaryotic DNA polymerase δ. If a wrong nucleotide is inserted opposite the *cis-syn* cyclobutane thymine dimer TT_3*, the erroneous nucleotides can be removed by 3'→5'-exonucleases. Therefore, with a high probability adenine will be inserted opposite thymine TT_3*. In this case the strand of DNA containing *cis-syn* cyclobutane thymine dimers TT_3* does not result in mutations. So many cycles of DNA replication can continue. However, if further DNA synthesis will involve DNA polymerases having a low fidelity of synthesis, there may be base substitution mutations. Moreover, they may be formed through many cycles of replication after DNA has been damaged. Consequently, these are the delayed mutations. *Cis-syn* cyclobutane thymine dimers TT_3* may result in targeted delayed transitions T-A→C-G, targeted delayed transversions T-A→G-C and T-A→A-T.[49,83] Opposite canonical thymine cytosine can be incorporated only. Canonical *cis-syn* cyclobutane thymine dimers TT may result in targeted delayed transversions T-A→G-C only.[49]

Polymerase tautomeric models for radiation induced bystander effects: untargeted mutagenesis during error-prone and SOS synthesis of double-stranded DNA, containing cis-syn cyclobutane thymine dimers

I proposed and develops the polymerase-tautomeric model for radiation-induced bystander effects.[87] The bystander effects are defined as the induction of cellular damage in unirradiated cells, induced by irradiated cells in the surrounding area.[18,24] Over 90% of the mutations arising in bystander cells were point mutations.[129,130] Radiation-induced bystander effects include only untargeted mutations.

Polymerase tautomeric models for untargeted base substitution mutations

Let us consider a site of DNA, on which *cis-syn* cyclobutane thymine dimers with bases in rare tautomeric forms appeared in both strands of DNA close to each other. Besides let us consider a site of DNA, on which in a small neighborhood of cyclobutane pyrimidine dimers with bases in the canonical tautomeric forms pairs base of adenine-thymine in rare tautomeric forms are formed. These sites are synthesized as a result of error-prone or SOS synthesis. Structural analysis indicates that canonical tautomeric forms of thymine cannot be incorporated opposite A_1*. But canonical tautomeric forms of cytosine or adenine can be incorporated opposite A_1*. Rare A_1* tautomer of adenine may result in a untargeted transition A-T→G-C or a untargeted homologous transversion A-T→T-A.[87] Molecule of thymine can be inserted opposite A_2* and A_4*[87] molecule of adenine can be inserted opposite T_3*[49] it is likely they will not result in mutations. The rare A_3*, A_5* and T_2* (Figure 4)[79,80] tautomers do not form hydrogen bonds with any canonical tautomers of DNA bases. So they cannot result in the base substitution mutations. Rare T_1* tautomer of thymine may result in A-T→G-C untargeted transition or A-T→T-A untargeted homologous transversion (Figure 3).[87] Molecules of the thymine in rare tautomeric form T_4* may result in transversion A-T→ C-G only.[87] Rare T_5* tautomer can result in transversion A-T→ C-G or homologous transversions A-T→T-A (Figure 3).[87]

Polymerase tautomeric models for untargeted insertions

The polymerase-tautomeric model for the mechanism of the formation of untargeted insertions caused by thymine and adenine in certain rare tautomeric forms is proposed.[85] Structural analysis indicates that opposite the rare tautomers of thymine T_2* (Figure 4) and adenine A_3* it is impossible to insert any canonical base so that hydrogen bonds between the rare tautomers of thymine T_2* or adenine A_3* and the canonical bases of DNA are formed. In doing so, author based on the following facts. Specialized or modified DNA polymerases can incorporate bases opposite DNA bases that are in rare tautomeric forms. Such bases can form hydrogen bonds with the bases of the template DNA, and canonical bases are, as a rule, incorporated. The error-prone and SOS synthesis of double-stranded DNA containing the rare tautomers T_2* or A_3* in one of its strands is considered. This synthesis will result in one-nucleotide gap opposite

thymine T_2* or adenine A_3*. On DNA sites with a homogenous nucleotide composition the end of the nascent DNA strand can slip. The end of the growing strand may form hydrogen bonds with a new site. A loop can form. As a result, the daughter strand is elongated leading to untargeted insertion (Figure 9).[85] The polymerase tautomeric model for bystander effects is able to explain the mechanisms formation for untargeted base substitution mutations and untargeted insertions.

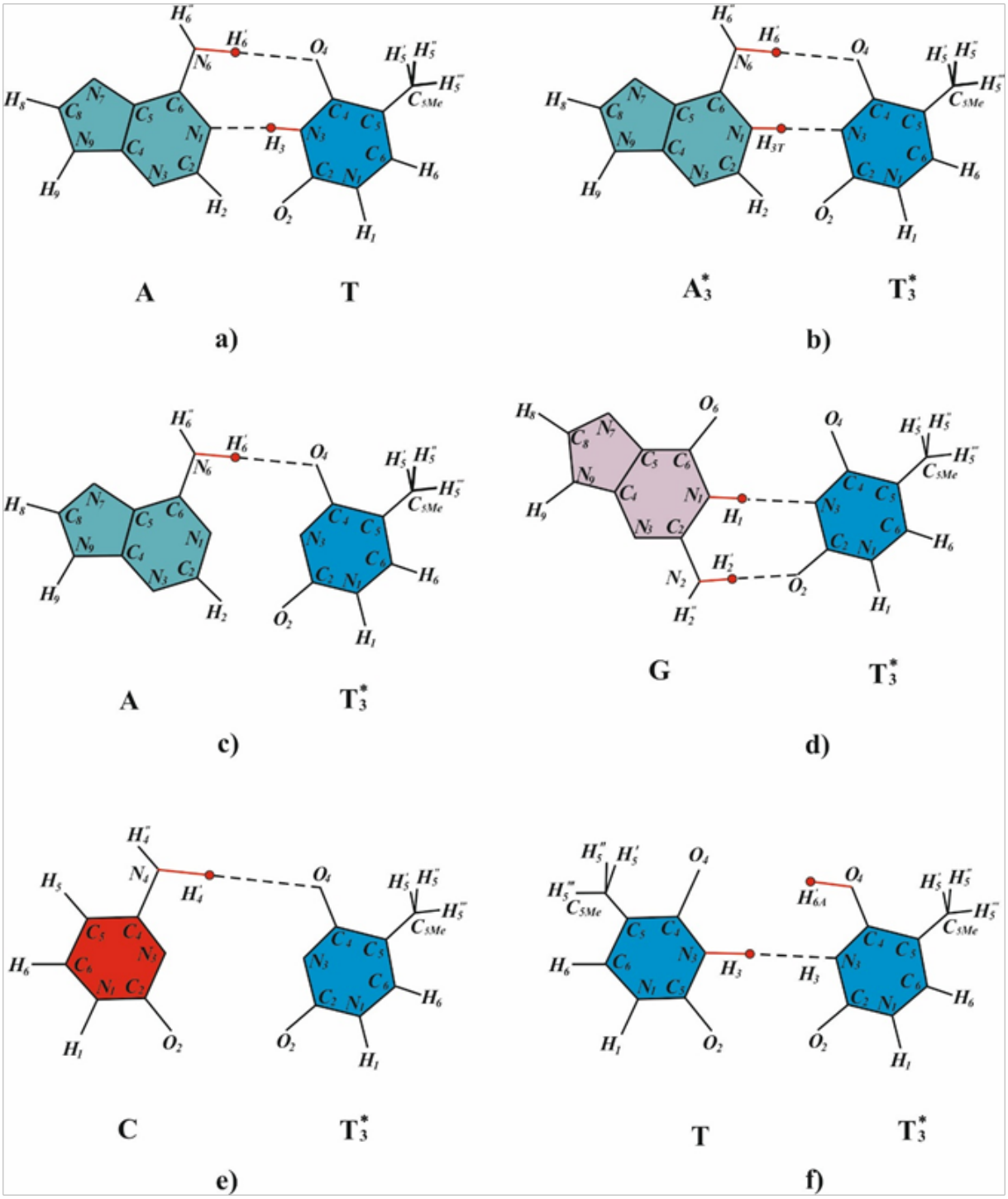

Figure 8 Rare tautomeric form for thymine T_3* and possible base pairs formed between thymine in rare T_3* tautomeric forms and bases in canonical tautomeric conformations: a) canonical adenine-thymine base pair; b) rare tautomeric forms of thymine T_3* and A_3* of adenine; c) – f) possible base pairs formed between thymine in rare T_3* tautomeric forms and bases in canonical tautomeric conformations: c) T_3* and adenine; d) T_3* and guanine; e) T_3* and cytosine; f) T_3* and thymine.[49]

Citation: Grebneva HA. Paradigm change in mutagenesis: polymerase tautomeric models for targeted, delayed and untargeted ultraviolet mutagenesis during error prone and SOS replication of double stranded DNA, containing *cis-syn* cyclobutane thymine dimers or thymine in rare tautomeric forms. *Int J Mol Biol Open Access.* 2019;4(1):1–15. DOI: 10.15406/ijmboa.2019.04.00091

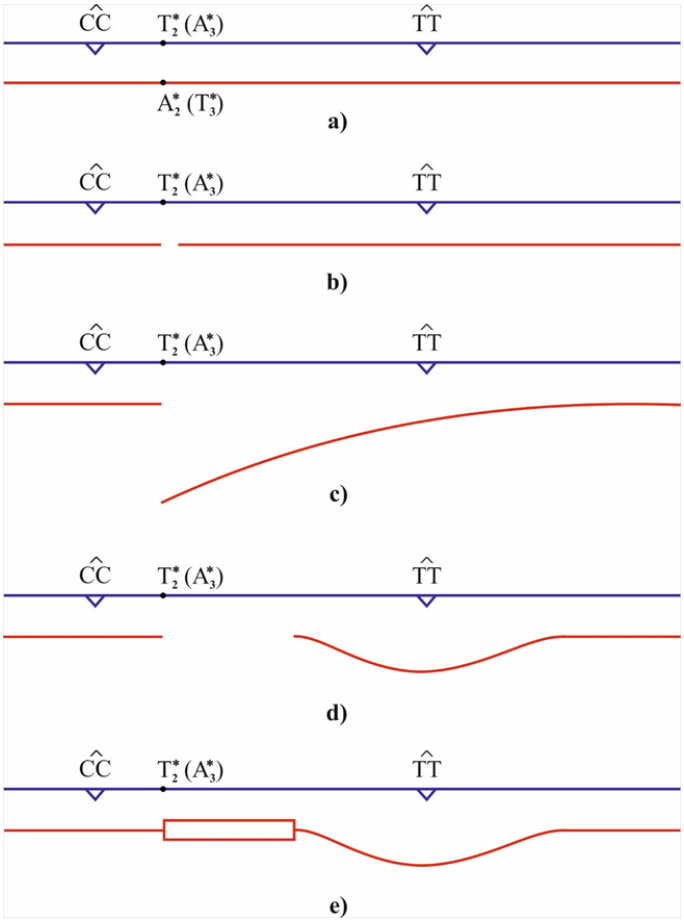

Figure 9 Formation of an untargeted insertions from several nucleotides. a) a DNA site containing 2 cyclobutane pyrimidine dimers and, next to them, the rare tautomer of thymine T_2* or the rare tautomer of adenine A_3*; b) a one-nucleotide gap arises opposite thymine T_2* or adenine A_3*; c) the end of the growing DNA strand slips; d) a loop is formed; e) the gap is filled in. In result an untargeted insertion of several nucleotides is produced.[85]

Conclusion

The modern theory of a UV-mutagenesis cannot exhaustively explain many phenomena, including the reason of formation of targeted, delayed and untargeted mutations. The polymerase-tautomeric model for targeted mutagenesis is able to explain the mechanisms formation for targeted substitution mutations,[42,76] targeted insertions,[42,79] targeted deletions[42,80] and targeted complex insertions.[42,81] The polymerase-tautomeric models for radiation induced genomic instability is able to explain the mechanisms formation for targeted delayed base substitution mutations.[42,86] The polymerase-tautomeric model for radiation-induced bystander effects is able to explain the mechanisms formation for untargeted substitution mutations[84] and untargeted insertions.[85] Untargeted mutations appear opposite DNA bases in rare tautomeric forms located, for example, near (2-3 bases) from cyclobutane dimers. It is observed a thymine-guanine (T•G)[61] and a cytosine-adenine (C•A)[62] base pairs with one of the bases in rare tautomeric forms in the active site of DNA polymerases. This results are an experimental verification of polymerase-tautomeric models.

Acknowledgments

None

Conflicts of interest

The author declares that there is no conflicts of interest.

References

1. Besaratinia A, Yoon JI, Schroeder C, et al. Wavelength dependence of ultraviolet radiation-induced DNA damage as determined by laser irradiation suggests that cyclobutane pyrimidine dimers are the principal DNA lesions produced by terrestrial sunlight. *FASEB J.* 2011;25(9):3079–3091.
2. Takasawa K, Masutani C, Hanaoka F, et al. Chemical synthesis and translesion replication of a *cis–syn* cyclobutane thymine–uracil dimer. *Nucl Acids Res.* 2004;32(5):1738–1745.
3. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. *Nature*. 1998;396(6712):643–649.
4. Davies RJ, Malone JF, Gan Y, et al. High-resolution crystal structure of the intermolecular d(TpA) thymine– adenine photo adduct and its mechanistic implications. *Nucleic Acids Res.* 2007;35(4):1048–1053.
5. Rochette PJ, Therrien JP, Drouin R, et al. UVA-induced cyclobutane pyrimidine dimers form predominantly at thymine–thymine dipyrimidines and correlate with the mutation spectrum in rodent cells. *Nucleic Acids Res*. 2003;31(11):2786–2794**.**
6. Hsu PH, Philip C, Hanawalt PC, et al. Nucleotide excision repair phenotype of human acute myeloid leukemia cell lines at various stages of differentiation. *Mutat Res.* 2007;614(1–2):3–15.
7. Besaratinia A, Kim SI, Pfeifer GP. Rapid repair of UVA-induced oxidized purines and persistence of UVB-induced dipyrimidine lesions determine the mutagenicity of sunlight in mouse cells. *FASEB J.* 2008;22(7):2379–2392.
8. Wang H, Hoffman PD, Lawrence C, et al. Testing excision models for responses of mismatch-repair systems to UV photoproducts in DNA. *Environ Mol Mutagen.* 2006;47(4):296–306.
9. Krutyakov VM. Eukaryotic error-prone DNA polymerases: the suggested roles in replication, repair, and mutagenesis. *Mol Biol (Mosk).* 2006;40(1):3–11.
10. Hendel A, Ziv O, Gueranger Q, et al. Reduced efficiency and increased mutagenicity of translation DNA synthesis across a TT cyclobutane pyrimidine dimer, but not a TT 6-4 photoproduct, in human cells lacking DNA polymerase η. *DNA Repair (Amst).* 2008;7(10):1636–1646.
11. Vasquez Del Carpio R, Silverstein TD, Lone S, et al. Role of human DNA polymerase k in extension opposite from a *cis-syn* thymine dimer. *J Mol Biol.* 2011;408(2):252–261.
12. Ikehata H, Kudo H, Masuda T, et al. UVA induces C→T transitions at methyl-CpG-associated dipyrimidine sites in mouse skin epidermis more frequently than UVB. *Mutagenesis.* 2003;18(6):511–519.
13. Santiago MJ, Alejandre Duran A, Ruiz Rubio M. Analysis of UV-induced mutation spectra in *Escherichia coli* by DNA polymerase η from Arabidopsis thaliana. *Mutation Research*. 2006;601(1–2):51–60.
14. Heidenreich E, Eisler H, Steinboeck F. Epistatic participation of REV1 and REV3 in the formation of UV-induced frame shift mutations in cell cycle-arrested yeast cells. *Mutat Res*. 2006;593(1–2):187–95.
15. Levine JG, Schaaper RM, DeMarini DM. Complex frame shift mutations mediated by plasmid pKM101: mutational mechanisms deduced from 4-aminobiphenyl-induced mutation spectra in *Salmonella*. *Genetics.* 1994;136(3):731–746.
16. Little JB, Gorgojo L, Vetrovs H. Delayed appearance of lethal and specific gene mutations in irradiated mammalian cells. *Int J Radiat Oncol Biol Phys.* 1990;19(6):1425–1429.

17. Boesen JJ, Stuivenberg S, Thyssens CH, et al. Stress response induced by DNA damage leads to specific, delayed and untargeted mutations. *Molecular and General Genetics*. 1992;234(2):217–227.

18. Little JB. Genomic instability and bystander effects: a historical perspective. *Oncogene*. 2003;22(45):6978–6987.

19. Harper K, Lorimore SA, Wright EG. Delayed appearance of radiation induced mutations at the Hprt locus in murine hemopoietic cells. *Exp Hematol.* 1997;25(3):263–269.

20. Lawrence CW, Banerjee SK, Borden A, et al. T-T cyclobutane dimers are misinstructive, rather than non-instructive, mutagenic lesions. *Mol Gen Genet.* 1990;222(1):166–168.

21. Lawrence CW, Gibbs PE, Borden A, et al. Mutagenesis induced by single UV photoproducts in *E. coli* and yeast. *Mutat Res.* 1993;299(3–4):157–163.

22. Brotcorne Lannoye A, Maenhaut Michel G. Role of RecA protein in untargeted UV mutagenesis of bacteriophage λ: evidence for requirement for the dinB gene. *Proc Natl Acad Sci USA.* 1986;83(11):3904–3908.

23. Stamato TD, Perez ML. EMS and UV-light-induced colony sectoring and delayed mutation in Chinese hamster cells. *Int J Radiat Biol.* 1998;74(6):739–745.

24. Whiteside JR, Allinson SL, Trevor J, et al. Timeframes of UVA-induced bystander effects in human keratinocytes. *Photochem Photobiol.* 2011;87(2):435–440.

25. Little JB, Nagasawa H, Pfenning T, et al. Radiation-induced genomic instability: delayed mutagenic and cytogenetic effects of X rays and alpha particles. *Radiat Res.* 1997;148(4):299–307.

26. Okazaki R, Ootsuyama A. P53-dependent delayed effects of radiation vary according to time of irradiation of p53+/- mice. *J Radiat Res.* 2014;55(1):25–31.

27. Tang M, Pham P, Shen X, et al. Roles of *Escherichia coli* DNA polymerase IV and V in lesion-targeted and untargeted SOS mutagenesis. *Nature.* 2000;404(6781):1014–1018.

28. Taylor JS. New structural and mechanistic insight into the A-rule and the instructional and non-instructional behavior of DNA photoproducts and other lesions. *Mutat Res.* 2000;510(1–2):55–70.

29. Rünger TM, Kappes UP. Mechanisms of mutation formation with long-wave ultraviolet light (UVA). *Photodermatology, Photoimmunology Photomed.* 2008;24(1):2–10.

30. Song Q, Cannistraro V, Taylor JS. Synergistic modulation of cyclobutane pyrimidine dimer photoproduct formation and determination at a TmCG site over a full helical DNA turn in a nucleosome core particle. *Nucl Acids Res*. 2014;42(21):13122–13133.

31. Cannistraro VJ, Pondugula S, Song Q, et al. Rapid deamination of cyclobutane pyrimidine dimer photoproducts at TCG sites in a translationally and rotationally positioned nucleosome *in Vivo*. *J Biol Chem*. 2015;290(44):26597–26609.

32. Song Q, Sherrer SM, Suo Z, et al. Preparation of site-specific T=mCG *cis-syn* cyclobutane dimer-containing template and its error-free bypass by yeast and human polymerase η. *J Biol Chem*. 2012;287(11):8021–8028.

33. Kozmin S, Slezak G, Reynaud Angelin A, et al. UVA radiation is highly mutagenic in cells that are unable to repair 7,8-dihydro-8-oxoguanine in *Saccharomyces* cerevisiae. *Proc Natl Acad Sci USA.* 2005;102(38):13538–13543.

34. Watson JD, Crick FHC. The structure of DNA. *Cold Spring Harbor Symp Quant Biol.* 1953;18:123–131.

35. Gorb L, Podolyan Y, Leszczynski J, et al. A quantum-dynamics study of the prototropic tautomerism of guanine and its contribution to spontaneous point mutations in *Escherichia coli*. *Biopolymers*. 2002;61(1):77–83.

36. Podolyan V, Gorb L, Leszczynski J. Ab initio study of the prototropic tautomerism of cytosine and guanine and their contribution to spontaneous point mutations. *Int J Mol Sci.* 2003;4(7):410–421.

37. Danilov VI, Anisimov VM, Kurita N, et al. MP2 and DFT studies of the DNA rare base pairs: the molecular mechanism of spontaneous substitution mutations conditioned by tautomerism of bases. *Chem Phys Lett*. 2005;412(4–6):285–293.

38. Harris VH1, Smith CL, Jonathan Cummins W, et al. The effect of tautomeric constant on the specificity of nucleotide incorporation during DNA replication: support for the rare tautomer hypothesis of substitution mutagenesis. *J Mol Biol*. 2003;326(5):1389–1401.

39. Ostapenko NI, Skryshevskii YuA, Kadashchuk AK, et al. Thermoluminescence of crystals of nuclein acids bases. *Izvestia Acad Sci USSR*. 1990;54:445–449.

40. Novak MJ, Lapinski L, Fulara J. Matrix isolation studies of cytosine: The separation of the infrared spectra of cytosine tautomers. *Spectrochim Acta*. 1989;45(2):229–242.

41. Grebneva HA. A Polymerase-tautomeric model for targeted substitution mutations formation during error-prone and SOS replication of double-stranded DNA, containing *cis-syn* cyclobutane cytosine dimers. *Int J Mol Biol Open Access*. 2016;1(1):4–17.

42. Grebneva HA. A Polymerase – Tautomeric Model for Targeted Frameshift Mutations: Deletions Formation during Error-prone or SOS Replication of Double-stranded DNA Containing *cis-syn* Cyclobutane Thymine Dimers. *Journal of Photonic Materials and Technology.* 2015;1(2):19–26.

43. Ikehata H, Ono T. The mechanisms of UV mutagenesis. *J Radiat Res.* 2011;52(2):115–125.

44. Horsfall MJ, Borden A, Lawrence CW. Mutagenic properties of the T-C cyclobutane dimer. *J Bacteriol*. 1997;179(9):2835–2839.

45. Wang Y, Woodgate R, McManus TP, et al. Evidence that in xeroderma pigmentosum variant cells, which lack DNA polymerase η, DNA polymerase ι causes the very high frequency and unique spectrum of UV-induced mutations. *Cancer Res.* 2007;67(7):3018–3026.

46. Auerbach P, Bennett RAO, Bailey EA, et al. Mutagenic specificity of endogenously generated abasic sites in *Saccharomyces cerevisiae* chromosomal DNA. *Proc Natl Acad Sci USA.* 2005;102(49):17711–17716.

47. Pagès V, Johnson RE, Prakash L, et al. Mutational specificity and genetic control of replicative bypass of an abasic site in yeast. *Proc Natl Acad Sci USA*. 2008;105(3):1170–1175.

48. Servant L, Cazaux C, Bieth A, et al. A role for DNA polymerase β in mutagenic UV lesion bypass. *J Biol Chem*. 2002;277(50):50046–50053.

49. Grebneva HA. A polymerase-tautomeric model for radiation-induced genomic instability: targeted delayed substitution mutations under error-prone and SOS synthesis of double-stranded DNA containing *cis-syn* cyclobutane thymine dimers. *Int J Mol Biol Open Access.* 2018;3(3):125–141.

50. Grebneva HA. *A-rule* during error-prone and SOS synthesis of DNA containing *cis-syn* cyclobutane thymine dimers in light of the polymerase-tautomeric model for targeted base substitution mutagenesis. The collection of "Thymine: Structure, Syntheses and Theories", 2019.

Citation: Grebneva HA. Paradigm change in mutagenesis: polymerase tautomeric models for targeted, delayed and untargeted ultraviolet mutagenesis during error prone and SOS replication of double stranded DNA, containing *cis-syn* cyclobutane thymine dimers or thymine in rare tautomeric forms. *Int J Mol Biol Open Access.* 2019;4(1):1–15. DOI: 10.15406/ijmboa.2019.04.00091

51. Nicolas E, Golemis EA, Arora S. POLD1: Central mediator of DNA replication and repair, and implication in cancer and other pathologies. *Gene*. 2016;590(1):128–141.

52. Krutyakov VM. Rational regulation of DNA polymerase-mediated mutagenesis and autonomous 3′®5′-exonucleases. *Mol Biol (Mosk)*. 1998;32(2):197–200.

53. Yang IY, Hashimoto K, de Wind N, et al. Two distinct translesion synthesis pathways across a lipid peroxidation-derived DNA adduct in mammalian cells. *J Biol Chem*. 2009;284(1):191–198.

54. Yang W, Woodgate R. What a difference a decade makes: insights into translesion DNA synthesis. *Proc Natl Acad Sci USA*. 2007;104(40):15591–15598.

55. Vaisman A, Woodgate R. Translesion DNA polymerases in eukaryotes: what makes them tick? *Crit Rev Biochem Mol Biol*. 2017;52(3):274–303.

56. Waters LS, Minesinger BK, Wiltrout ME, et al. Eukaryotic translesion polymerases and their roles and regulation in DNA damage tolerance. *Microbiol Mol Biol Rev.* 2009;73(1):134–154.

57. Cruet Hennequart S, Gallagher K, Sokol AM, et al. DNA polymerase eta, a key protein in translesion synthesis in human cells. *Subcell Biochem*. 2010;50:189–209.

58. Kanemaru Y, Suzuki T, Sassa A, et al. DNA polymerase kappa protects human cells against MMC-induced genotoxicity through error-free translesion DNA synthesis. *Genes Environ.* 2017;39:6.

59. Suzuki T, Gruz P, Honma M, et al. The role of DNA polymerase ζ in translesion synthesis across bulky DNA adducts and cross-links in human cells. *Mutat Res*. 2016;791–792:35–41.

60. Hawver LA, Gillooly CA, Beuning PJ. Characterization of *Escherichia coli* UmuC active-site loops identifies variants that confer UV hypersensitivity. *J Bacteriol*. 2011;193(19):5400–5411.

61. Bebenek K, Pedersen LC, Kunkel TA. Replication infidelity via a mismatch with Watson-Crick geometry. *Proc Natl Acad Sci USA*. 2011;108(5):1862–1867.

62. Wang W, Hellinga HW, Beese LS. Structural evidence for the rare tautomer hypothesis of spontaneous mutagenesis. *Proc Natl Acad Sci USA*. 2011;108(43):17644–17648.

63. HA Grebneva. The theory of thermal relaxation of the excitation energy of hydrogen bonds in a DNA molecule and its contribution to ultraviolet mutagenesis. 2019.

64. Grebneva HA. A new semiempirical potential function for hydrogen bonds and its possible use in studying the DNA molecule. *J Mol Struct*. 1993;296(1–2):127–132.

65. Tolpygo KB, Grebneva HA. Effect of the state of h-b-1 hydrogen bond of the character of some atom vibrations in guanine-cytosine pair of the DNA molecule. *Int J Quant Chem*. 1996;57(2):219–227.

66. Grebneva HA, Tolpygo KB. Crystalline and local vibrations of paired bases in poly (dG)-poly (dC) interacting with the h-b-1 hydrogen bond. *Int J Quant Chem*. 1997;62(1):115–124.

67. Grebneva HA, Tolpygo KB. The heat deexcitation of hydrogen bond protons in paired bases of DNA molecules. *Studia Biophysica*. 1990;135(1):115–125.

68. Tolpygo KB, Grebneva HA. Stationary states of the proton excitation at the DNA site consisting of guanine-cytosine pairs with a single "defect". *Ukr Phyz J.* 1993;38(6):855–861.

69. Grebneva HA. Nature and mechanisms of hot and cold spots of ultraviolet mutagenesis formation. *Dopovidi NAN Ukraine*. 2012;10: 181–187.

70. Grebneva HA. Targeted mutagenesis caused by cytosine dimers and mechanism substitution mutation formation under SOS-replication after irradiation double-stranded DNA by ultraviolet light. *Dopovidi NAN Ukraine*. 2001;(8):183–189.

71. Grebneva HA, Ivanov MO. The possible molecular mechanisms of untargeted type mutation under SOS replication of double-stranded DNA. *Biopolymers Cell.* 2001;17(5):388–395.

72. Grebneva HA. The molecular mechanisms derivation of mutation bases alteration after a post replication SOS-repair a DNA containing thymine dimers. *Biopolymers Cell*. 2001;17(6):487–500.

73. Grebneva HA. The nature and possible mechanisms of potential mutations formation due to the appearance of thymine dimers after irradiating double-stranded DNA by ultra-violet light. *Biopolymers Cell*. 2002;18(1):205–218.

74. Grebneva HA. Possible molecular mechanisms of untargeted mutagenesis upon a post-replication SOS repair after irradiating double-stranded DNA by ultraviolet light. *Biopolymers Cell.* 2002;18(5):394–400.

75. Grebneva HA. Nature and possible mechanisms formation of potential mutations arising at emerging of thymine dimers after irradiation of double-stranded DNA by ultraviolet light. *J Molec Struct.* 2003;645(2–3):133–143.

76. Grebneva HA. A model for targeted substitution mutagenesis during SOS replication of double-stranded DNA containing *cis-syn* cyclobutane thymine dimers. *Environ Mol Mutagen*. 2006;47(9):733–745.

77. Grebneva HA. Three sources of untargeted substitution mutations arising under irradiation DNA molecule by ultraviolet light. *Dopovidi NAN Ukraine.* 2013;(1):143–150.

78. Grebneva HA. Mechanisms targeted insertions formation under synthesis of DNA molecule containing *cis-syn* cyclobutane cytosine dimers. *Dopovidi NAN Ukraine*. 2014;(11):156–164.

79. Grebneva HA. Mechanisms of targeted frameshift mutations – insertion formation under error-prone or SOS synthesis of DNA containing *cis-syn* cyclobutane thymine dimers. *Mol Biol (Mosk.)* 2014;48(4):457–467.

80. Grebneva HA. A polymerase – tautomeric model for targeted frameshift mutations: deletions formation during error-prone or SOS replication of double-stranded DNA containing *cis-syn* cyclobutane thymine dimers. *J Phot Mat Technology*. 2015;1(2):19–26.

81. Grebneva HA. Mechanisms of targeted complex insertions formation under synthesis of DNA molecule containing *cis-syn* cyclobutane thymine dimers. *Dopovidi NAN Ukraine.* 2015;(5):145–154.

82. Grebneva HA. Mechanisms targeted deletions formation under synthesis of DNA molecule containing *cis-syn* cyclobutane thymine dimers. *Dopovidi NAN Ukraine.* 2015;(4):124–132.

83. Grebneva HA. Polymerase-tautomeric model for mechanism of targeted delayed substitution mutations formation under synthesis of DNA containing *cis-syn* cyclobutane thymine dimers. *Dopovidi NAN Ukraine*. 2016;(5):101–109.

84. Grebneva HA. A polymerase–tautomeric model for radiation-induced bystander effects: a model for untargeted substitution mutagenesis during error-prone and SOS replication of double-stranded DNA containing thymine and adenine in rare tautomeric forms. *Int J Mol Biol Open Access*. 2017;2(2):63–74.

85. Grebneva HA. A polymerase-tautomeric model for radiation-induced bystander effects: a model for untargeted insertional mutagenesis during error-prone and SOS synthesis of double-stranded DNA containing thymine in the rare tautomeric form. 2017.

Citation: Grebneva HA. Paradigm change in mutagenesis: polymerase tautomeric models for targeted, delayed and untargeted ultraviolet mutagenesis during error prone and SOS replication of double stranded DNA, containing *cis-syn* cyclobutane thymine dimers or thymine in rare tautomeric forms. *Int J Mol Biol Open Access*. 2019;4(1):1–15. DOI: 10.15406/ijmboa.2019.04.00091

86. Grebneva HA. A polymerase-tautomeric model for radiation-induced genomic instability: targeted delayed substitution mutations during error-prone and SOS replication of double-stranded DNA, containing *cis-syn* cyclobutane cytosine dimers. 2018.

87. Grebneva HA. Symptoms of crisis in mutagenesis and ways of its resolution. 2018.

88. Park HJ, Zang K, Ren Y, et al. Crystal structure of a DNA decamer containing a *cis-syn* thymine dimer. *Proc Natl Acad Sci USA*. 2002;99(25):15965–15970.

89. Bdour HM, Kao JL, Taylor JS. Synthesis and characterization of a [3-15N]-labeled *cis-syn* thymine dimer-containing DNA duplex. *J Org Chem*. 2006;71(4):1640–1646.

90. Grebneva HA. DNA irradiation with ultraviolet light. Potential alterations and mutations. *Molecular Biology (Mosk)*. 1994;28(4):527–532.

91. Grebneva HA. Proton potential for broad spectrum of hydrogen bond length in water dimer. *Zhurnal Strukturnoy Khimii.* 1997;38(3):422–430.

92. Hovorun DM. A structural-dynamic model on spontaneous semi open states in DNA. *Biopolymers and Cell*. 1997;13(1):39–45.

93. Khare V, Eckert KA. The proofreading 3′ → 5′ exonuclease activity of DNA polymerases: a kinetic barrier to translesion DNA synthesis. *Mutat Res.* 2002;510(1–2):45–54.

94. Yarosh DB. Enhanced DNA repair of cyclobutane pyrimidine dimers changes the biological response to UV-B radiation. *Mutat Res*. 2002;509(1–2):221–226.

95. Timms AR, Bridges BA. DNA polymerase V-dependent mutator activity in an SOS-induced *Escherichia coli* strain with a temperature-sensitive DNA polymerase III. *Mutat Res.* 2002;499(1–2):97–101.

96. Kuriyan J, O Donnell M. Sliding clamps of DNA polymerases. *J Molec Biol*. 1993;234(4):915–925.

97. Stillman B. Smart machines at the DNA replication fork. *Cell.* 1994;78(5):725–728.

98. Schurtenberger P, Egelhaaf SU, Hindges R, et al. The solution structure of functionally active human proliferating cell nuclear antigen determined by small-angle neutron scattering. *J Molec Biol*. 1998;275(1):123–132.

99. Cox LS. Who binds wins: competition for PCNA rings out cell-cycle changes. *Trends Cell Biol*. 1997;7(12):493–498.

100. Woodgate R. A plethora of lesion-replicating DNA polymerases. *Genes* Dev.1999;13:2191–2195.

101. Prelich G, Tan CK, Kostura M, et al. Functional identity of proliferating cell nuclear antigen and a DNA polymerase auxiliary protein. *Nature*. 1987;326(6112):517–520.

102. Bravo R, Frank R, Blundell PA, et al. Cyclin/PCNA is the auxiliary protein of DNA polymerase delta. *Nature*. 1987;326(6112):515–517.

103. LeClerc JE, Borden A, Lawrence CW. The thymine-thymine pyrimidine-pyrimidine (6-4) ultraviolet light photoproduct is highly mutagenic and specifically induces 3' thymine-to-cytosine transitions in *Escherichia coli*. *Proc Natl Acad Sci USA*. 1991;88(21):9685–9689.

104. Kunkel TA, Bebenek R. DNA replication fidelity. *Annu Rev Biochem*. 2000;69:497–529.

105. Shibutani S, Takeshita M, Grollman AP. Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxoG. *Nature*. 1991;349(6308):431–434.

106. Kim SR, Matsui K, Yamada P, et al. Roles of chromosomal and episomal *dinB* genes encoding Pol IV in targeted and untargeted mutagenesis in *Escherichia coli*. *Mol Genet Genomics*. 2001;266(2):207–215.

107. Wang C, Taylor JS. *In vitro* evidence that UV-induced frameshift and substitution mutations at T tracts are the result of misalignment-mediated replication past a specific thymine dimer. *Biochem.* 1992;31(14):3671–3681.

108. Streisinger G, Okada J, Emerich J, et al. Frame shift mutations and the genetic code. *Cold Spring Harb Symp Quant Biol.* 1966;31:77–84.

109. Strand M, Prolla TA, Liskay RM, et al. Destabilization of tracts of simple repetitive DNA in yeast by mutations affecting DNA mismatch repair. *Nature*. 1993;365(6443):274–276.

110. Bzymek M, Saveson CJ, Feschenko VV, et al. Slipped misalignment mechanisms of deletion formation: *in vivo* susceptibility to nucleases. *J Bacteriol*. 1999;181(2):477–482.

111. Baase WA, Jose D, Ponedel BC, et al. DNA models of trinucleotide frameshift deletions: the formation of loops and bulges at the primer-template junction. *Nucleic Acids Research*. 2009;37(5):1682–1689.

112. Kobayashi S, Valentine MR, Pham P, et al. Fidelity of *Escherichia coli* DNA polymerase IV. Preferential generation of small deletion mutations by dNTP-stabilized misalignment. *J Biol Chem.* 2002;277(37):34198–34207.

113. Raghunathan G, Kieber Emmons T, Rein R, et al. Conformation features of DNA containing a *cis-syn* photodimer. *J Biopol Struct Dyn.* 1990;7(4):899–913.

114. Cooney MG, Miller JH. Calculated distortions of duplex DNA by a cis, syn cyclobutane thymine dimer are unaffected by a 3' TpA step. *Nucleic Acids Res.* 1997;25(7):1432–1436.

115. McAteer K, Jing Y, Kao J, et al. Solution-state structure of a DNA dodecamer duplex containing a *cis-syn* thymine cyclobutane dimer, the major UV photoproduct of DNA. *J Molec Biol*. 1998;282(5):1013–1032.

116. Yamaguchi H, Van Aalten DM, Pinak M, et al. Essential dynamics of DNA containing a cis.syn cyclobutane thymine dimer lesion. *Nucleic Acids Res.* 1998;26(8):1939–1946.

117. DeMarini DM, Shelton ML, Abu Shakra A, et al. Spectra of spontaneous frameshift mutations at the hisD3052 allele of *salmonella* typhimurium in four DNA repair backgrounds. *Genetics.* 1998;149(1):17–36.

118. Papanicolaou C, Ripley LS. Polymerase-specific differences in the DNA intermediates of frameshift mutagenesis. *In vitro* synthesis errors of *Escherichia coli* DNA polymerase I and its large fragment derivative. *J Mol Biol*. 1989;207(2):335–353.

119. DeMarini DM. Influence of DNA repair on mutation spectra in *Salmonella*. *Mutat Res*. 2000;450(1–2):5–17.

120. Allen CP, Fujimori A, Okayasu R, et al. Radiation induced delayed genome instability and hypermutation in mammalian cells. In: Mittelman D, editor. Stress induced mutagenesis. Springer: New York; 2013:183–198.

121. Sargentini NJ, Smith KC. Ionizing and ultraviolet radiation-induced reversion of sequenced frameshift mutations in *Escherichia coli*: a new role for umuDC suggested by delayed photoreactivation. *Mutat Res*. 1987;179(1):55–63.

122. Ullrich RL, Ponnaiya B. Radiation-induced instability and its relation to radiation carcinogenesis. *Int J Radiat Biol*. 1998;74(6):747–754.

123. Little JB. Radiation carcinogenesis. *Carcinogenesis*. 2017;21(3):397–404.

124. Karotki AV, Baverstock K. What mechanisms/processes underlie radiation-induced genomic instability? *Cell Mol Life Sci*. 2012;69(20):3351–3360.

125. Durant ST, Paffet, KS, Shrivastav M, et al. UV radiation induces delayed hyperrecombination associated with hypermutation in human cells. *Mol Cell Biol*. 2006;26(16):6047–6055.

126. Niwa O. Radiation induced dynamic mutations and transgenerational effects. *J Radiat Res*. 2006;47(B):25–30.

127. Suzuki K, Ojima M, Kodama S, et al. Radiation-induced DNA damage and delayed induced genomic instability. *Oncogene*. 2003;22(45):6988–6993.

128. Dahle J, Kaalhus O, Stokke T, et al. Bystander effects may modulate ultraviolet A and B radiation-induced delayed mutagenesis. *Radiat Res*. 2005;163(3):289–295.

129. Huo L, Nagasawa H, Little JB. *HPRT* mutants induced in bystander cells by very low fluences of α particles result primarily from point mutations. *Radiat Res*. 2001;156(5 Pt 1):521–525.

130. Kinashi Y, Suzuki M, Masunaga S, et al. Bystander effect-induced mutagenicity in HPRT locus of CHO cells following BNCT neutron irradiation: Characteristics of point mutations by sequence analysis. *Appl Radiat Isot*. 2009;67(7-8 Suppl):325–327.

Citation: Grebneva HA. Paradigm change in mutagenesis: polymerase tautomeric models for targeted, delayed and untargeted ultraviolet mutagenesis during error prone and SOS replication of double stranded DNA, containing *cis-syn* cyclobutane thymine dimers or thymine in rare tautomeric forms. *Int J Mol Biol Open Access*. 2019;4(1):1–15. DOI: 10.15406/ijmboa.2019.04.00091