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Polymerase-tautomeric Model for Untargeted Delayed Base Substitution Mutations Formation during Error-prone and SOS Replication of Double-stranded DNA Containing Thymine and Adenine in Some Rare Tautomeric Forms

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ABSTRACT

Polymerase-tautomeric model for untargeted delayed base substitution mutations is proposed. Structural analysis of bases insertion showed that any canonical bases may be inserted opposite rare tautomeric forms of thymine T_3^* , adenines A_2^* and A_4^* so that between them hydrogen bonds are formed. Canonical adenine and cytosine can be incorporated opposite canonical thymine only. Canonical thymine and guanine can be incorporated opposite canonical adenine only. If in the synthesis of DNA containing rare tautomeric forms of thymine T_3^* , adenines A_2^* and A_4^* , 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. It was shown that the conclusion made in the Tomasetti and Vogelstein cancer risk model that the formation of about 67% of all mutations was not caused by exposure to any mutagens is erroneous.

1. Introduction

The mutations formation is the main cause of cancer^[1,2]. Untargeted delayed base substitution mutations are delayed base substitution mutations are formed on so-called undamaged DNA sites. They are part of radiation-induced genomic instability^[3]. Radiation-induced genomic instability result in radiation-induced cancer^[4,5]. Untargeted mutations are mutations that appear on the so-called undamaged sites of DNA

^[6-16]. Untargeted and untargeted delayed mutations are considered as radiation-induced bystander effects^[17-20]. The generally accepted polymerase paradigm assumes that opposite DNA damage DNA polymerases incorporate bases that are unable to form hydrogen bonds with matrix bases^[6,7,21-25].

Based on experimental facts, let's analyze polymerase paradigm of mutagenesis. An analysis of the work of various DNA polymerases showed^[26] that specialized and modified DNA polymerases incorporate canonical

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bases opposite cyclobutane pyrimidine dimers, capable of forming hydrogen bonds with matrix bases. Several works^[27-29], performed in recent years, were devoted to testing the tautomeric hypothesis of Watson and Crick^[30]. In the active centers of DNA polymerases, noncanonical base pairs of guanine – thymine^[27] and cytosine – adenine^[28] were found, one of the bases in each pair being in a rare tautomeric form. Therefore, experiments show that always, even with error-prone or SOS DNA synthesis, complementary base pairing occurs, but one of the bases may be in a rare tautomeric form. The hypothesis that noncomplementary base pairing occurs is contrary to these experimental facts. Thus, within the framework of the generally accepted polymerase paradigm, it is impossible to explain the mechanisms of formation of targeted and untargeted base substitution mutations^[26,31-33].

The Streisinger model^[34] is used to explain frameshift mutations^[35-37]. However, within the framework of the polymerase paradigm, it is absolutely not clear how *cis-syn* cyclobutane pyrimidine dimers can lead to frameshift mutations, and why, in some cases, they cause base substitution mutations, and in others, frameshift mutations. Within the framework of the polymerase paradigm, there is no complete understanding of the mechanisms of the targeted insertions^[38,39], targeted deletions^[40,41], and targeted complex mutations formation^[42]. Several explanations have been proposed for radiation-induced bystander effects^[3,20,43,44]. It is concluded that the nature and mechanisms of the formation of radiation-induced bystander effects are not fully understood^[3,20,43,44]. The nature of delayed mutations are not known^[3,43,45].

An analysis of the currently available models of mutagenesis shows that, within the framework of the generally accepted polymerase paradigm, it is not possible to exhaustively explain the mechanisms of the formation of any mutations. Therefore, to solve the problems of mutagenesis, a fundamentally different approach should be tried. In 1953, Watson and Crick suggested that mutagenesis may be based on the ability of DNA bases to be in various tautomeric forms^[30]. In the future, this idea is being actively developed^[46-51].

I have proposed and are developing polymerase-tautomeric models of targeted ultraviolet mutagenesis^[26,31,33,38-42,52-57], radiation-induced bystander effects^[58-62], and radiation-induced genomic instability^[32,52,62-66]. I proposed a mechanism for rare tautomeric forms of DNA bases formation^[33,68-70]. The formation of five rare tautomeric states of thymine and adenine^[33,56,57] and seven of guanine and cytosine^[31,71,72] is possible. DNA

bases can form rare tautomeric forms as a result of the fact that hydrogen atoms between the bases can pass to their partners in hydrogen bonds^[33,56,57]. They are also preserved during DNA synthesis - at the moment when such photodimers are in a single strand and therefore come into contact with water molecules for some time^[33,57].

As shown by quantum chemical calculations, as a rule, hydrogen atoms return to their original position^[73-77]. But opposite cyclobutane pyrimidine dimers, the DNA strand is bent and the hydrogen bonds between the bases that make up cyclobutane dimers or the bases adjacent to the photodimers are significantly weakened or are broken^[78-82]. Therefore, hydrogen atoms between bases located in different DNA strands that formed pairs cannot return to their previous partners in hydrogen bonds, they will remain in new positions. This means that the tautomeric state has changed in these bases, and it will be stable^[31,33,56,57,71,72]. To justify the polymerase-tautomeric models, K. B. Tolpygo and I performed several cycles of quantum-mechanical calculations devoted to studying the properties of excited hydrogen bonds in DNA^[52,83-87].

I developed mechanisms for targeted base substitution mutations formation^[26,32,33,52,55,66], targeted insertions^[32,33,39,66], targeted deletions^[32,33,40,41,66], delayed targeted base substitution mutations^[63,64,66] and targeted complex insertions^[32,33,42,66] under error-prone and SOS synthesis of DNA containing *cis-syn* cyclobutane thymine dimers. Mechanisms have been developed for formation of targeted base substitution mutations^[31,54] and frameshift mutations (insertion)^[38] with error-prone and SOS synthesis of DNA containing *cis-syn* cyclobutane cytosine dimers. In addition, a mechanism was proposed for formation of hot and cold spots of ultraviolet mutagenesis^[53].

The formation of five *cis-syn* cyclobutane thymine dimers TT₁*, TT₂*, TT₃*, TT₄* and TT₅*, containing thymine molecules in rare tautomeric forms is possible^[57]. *Cis-syn* cyclobutane thymine dimers TT₁*, TT₄* and TT₅* can cause only targeted base substitution mutations^[26,32,33,66]. *Cis-syn* TT₂* cyclobutane thymine dimers can lead to targeted insertions^[32,33,38,39,66] or targeted deletions only^[32,33,40,41,66]. *Cis-syn* TT₃* cyclobutane thymine dimers can cause delayed targeted base substitution mutations only^[63,64,66]. A DNA site containing *cis-syn* cyclobutane thymine dimers with thymine molecules in various tautomeric forms can lead to complex targeted mutations, for example, complex insertions^[32,33,42].

I developed mechanisms for untargeted base substitution mutations formation^[32,58-61,66] and untargeted

insertions^[32,62]. Their source is DNA bases in certain rare tautomeric forms located in small neighborhoods of cyclobutane dimers^[58-62]. A detailed substantiation of the untargeted mutations is given in Ref.^[61]. I developed a mechanism for the formation of targeted delayed base substitution mutations caused by *cis-syn* cyclobutane thymine dimers^[32,52,63,64,66] and cytosine dimers^[65].

Experimental studies in which noncanonical base pairs of guanine – thymine^[27] and cytosine – adenine^[28] with one of the bases in rare tautomeric forms were found in the active centers of DNA polymerases unambiguously demonstrate that tautomeric base pairs can form in active sites of polymerase^[27,28]. This provides strong support for the ideas of Watson and Crick^[30] and the polymerase-tautomeric models for mutagenesis through direct structural evidence^[27,28].

Ultraviolet light induces delayed mutations^[17,89]. The delayed mutations are usually point mutations^[88], delayed mutations is usually not removed^[90]. The genomic instability results in cancer^[91]. The mechanism of delayed mutations formation is not clear^[3,92-96]. Let us examine how untargeted delayed base substitution mutations can form.

2. Features of DNA Synthesis

DNA polymerases insert DNA bases opposite damaged DNA sites^[97]. Translesion synthesis can cause mutations^[99]. Mutations can form as a result of the mechanism of the sliding clamp^[100] or by the operation of low synthesis accuracy specialized DNA polymerases^[7,101] (more detail see in Ref.^[58]).

In order to understand how untargeted delayed base substitution mutations can be formed, we must understand how untargeted base substitution mutations are formed and how targeted delayed base substitution mutations are formed.

3. Polymerase-tautomeric Model for Untargeted Delayed Base Substitution Mutations During Error-prone or SOS Synthesis of Double-stranded DNA Containing Thymine and Adenine Molecules in T_3^* , A_2^* and A_4^* Rare Tautomeric Forms

As I have shown^[58-62], the source of the so-called untargeted mutations are DNA bases in rare tautomeric forms. The rare tautomeric forms of bases will be stable if these bases are located in small (3-5 bases) neighborhoods from DNA damage, for example, cyclobutane pyrimidine dimers and during DNA synthesis^[61].

Bases bonded to each other by hydrogen bonds

can change their tautomeric states if one or more hydrogen atoms pass in H-bonds^[57]. If, the lengths of the hydrogen bonds increase, then a second minimum appears^[102] and the hydrogen atoms cannot return to their previous positions. In other words, the bases will change their tautomeric states, they will turn into rare tautomeric states, and they are stable^[57]. Of course, they will be stable in all cases when the DNA strand opposite the damage is bent. Consequently, only bases in rare tautomeric forms, when H-bonds between the bases are lengthened or even torn, can lead to untargeted mutations.

As I have shown^[32,52,62-66], *cis-syn* cyclobutane pyrimidine dimers, one or both of which are in certain rare tautomeric forms, lead to targeted delayed base substitution mutations. Moreover, under certain conditions, even canonical *cis-syn* cyclobutane pyrimidine dimers can cause targeted delayed base substitution mutations^[32,52,62,63,65,66]. It turned out that bases in tautomeric forms can lead to delayed mutations only if such bases can form both canonical base pairs and non-canonical base pairs^[32,52,62-66].

Therefore, let us examine what mutations can appear opposite thymine and adenine molecules in the T_3^* , A_2^* and A_4^* rare tautomeric forms. DNA bases in rare tautomeric forms can appear upon irradiation of a DNA molecule with ultraviolet light^[103]. Mutations are always formed during DNA synthesis in error-prone or SOS replication, repair, or transcription processes^[104-111].

Let's explore of the canonical bases incorporation opposite matrix bases, based on the fact^[26] that specialized and modified DNA polymerases insert such canonical bases opposite matrix bases that are capable of forming H-bonds with matrix bases. As can be seen from Figure 1c, thymine T_3^* can form one hydrogen bonds with adenine, guanine (Figure 1d), cytosine (Figure 1e) and thymine (Figure 1f). Adenine in the A_2^* rare tautomeric form can form one hydrogen bond with thymine (Figure 2c), guanine (Figure 2e), cytosine (Figure 2d) and adenine (Figure 2f). Adenine in the A_4^* rare tautomeric form can form one hydrogen bond with thymine (Figure 3c). But it can form one hydrogen bond with guanine (Figure 3d).

Consider a DNA site (Figure 4a), one strand of which contains one canonical *cis-syn* cyclobutane thymine dimer TT, and in a small vicinity of it there is thymine in the T_3^* rare tautomeric form (Figure 1b), adenine molecules in A_2^* (Figure 2b) and A_4^* rare tautomeric forms (Figure 3b), as well as canonical thymine. Let other *cis-syn* cyclobutane pyrimidine dimers and other damage to the DNA molecule be quite far from it.

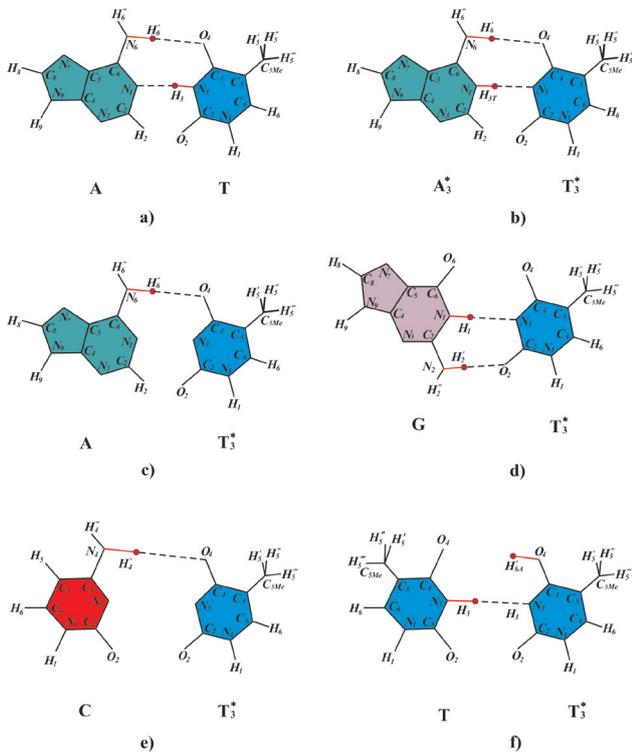


Figure 1. Rare tautomeric state of T_3^* thymine and structural analysis of pairing of thymine T_3^* with canonical DNA bases

Note: (a) thymine (T) and adenine (A) are in canonical tautomeric forms; (b) rare tautomeric forms of thymine T_3^* and adenine A_3^* ; (c) - (f) structural analysis of pairing of thymine T_3^* with canonical DNA bases: (c) with adenine; (d) with guanine; (e) with cytosine; (f) with thymine.

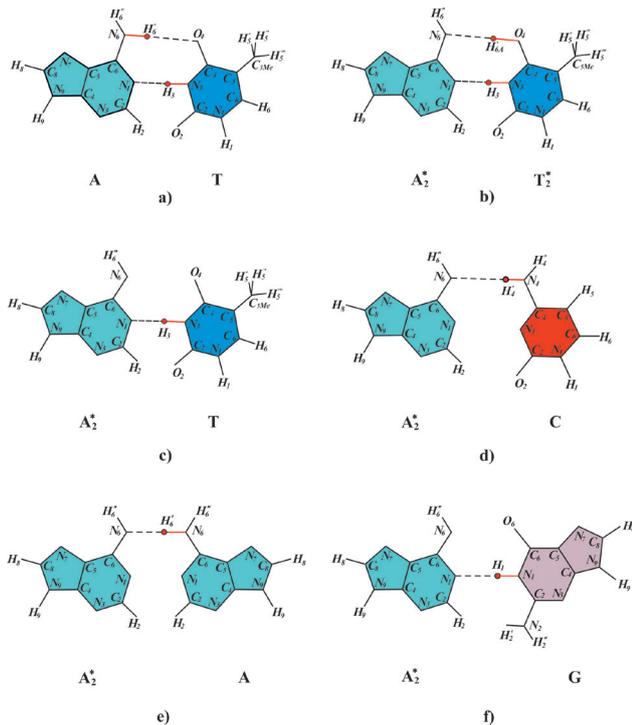


Figure 2. Rare tautomeric state A_2^* of adenine and structural analysis of pairing of adenine A_2^* with canonical DNA bases

tural analysis of pairing of adenine A_2^* with canonical DNA bases

Note: (a) thymine (T) and adenine (A) are in canonical tautomeric forms; (b) rare tautomeric forms of adenine A_2^* and thymine T_2^* ; (c) - (f) structural analysis of pairing of adenine A_2^* with canonical DNA bases: (c) with thymine; (d) with cytosine; (e) with adenine; (f) with guanine.

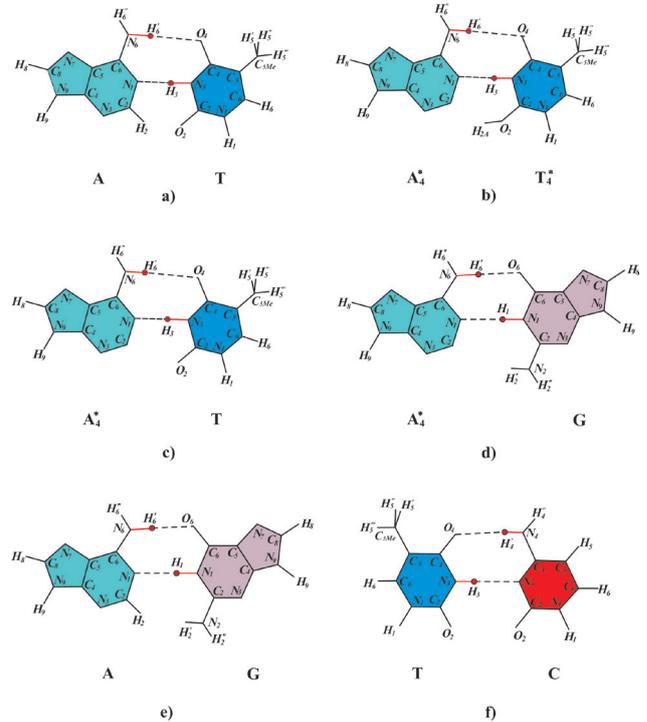


Figure 3. Rare tautomeric state A_4^* of adenine and structural analysis of pairing of adenine A_4^* , canonical adenine and thymine with canonical DNA bases

Note: (a) thymine (T) and adenine (A) are in canonical tautomeric forms; (b) rare tautomeric forms of adenine A_4^* and thymine T_4^* ; (c) structural analysis of pairing of adenine A_4^* with canonical thymine; (d) structural analysis of pairing of adenine A_4^* with cytosine; (e) structural analysis of pairing of canonical adenine with canonical thymine; (f) structural analysis of pairing of canonical thymine with canonical cytosine.

Since damage capable of stopping DNA synthesis is only one, translesion synthesis will be carried out using DNA polymerase conduct error-free DNA synthesis. Adenine will be inserted opposite thymine T_3^* . In this case, the mutation does not form (Figure 4c). For the same reasons, thymine will be inserted opposite adenine in rare tautomeric forms A_2^* and A_4^* (Figure 4b). In this case, mutations also do not form (Figure 4c). So many cycles of DNA replication can continue. Mutations will not appear until the situation changes.

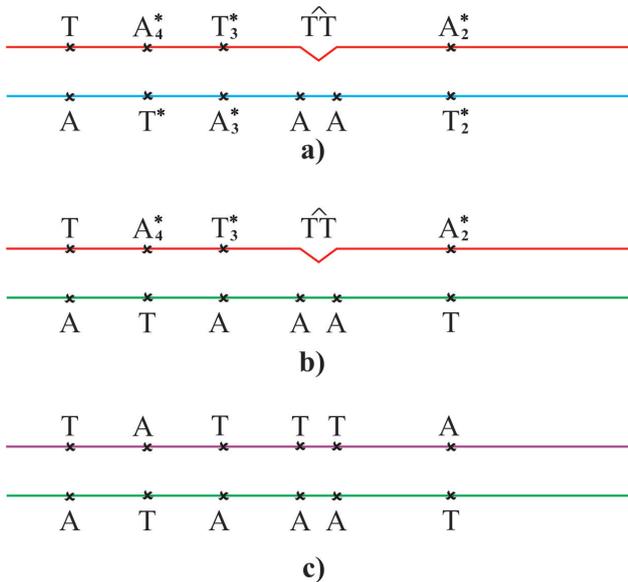


Figure 4. Error-prone or SOS-replication of the DNA containing canonical thymine, thymine in rare tautomeric form T₃^{*}, molecules of adenine in rare tautomeric forms A₂^{*} and A₄^{*} located in a small neighborhood of the *cis-syn* cyclobutane thymine dimer TT. Molecules of thymine in rare tautomeric form T₃^{*}, molecules of adenine in rare tautomeric forms A₂^{*} and A₄^{*} do not result in mutations

Note: (a) a DNA site containing canonical thymine, thymine in rare tautomeric form T₃^{*}, molecules of adenine in rare tautomeric forms A₂^{*} and A₄^{*} located in a small neighborhood of the *cis-syn* cyclobutane thymine dimer TT; (b) adenine molecules are inserted opposite the thymine in the rare tautomeric form of T₃^{*} and canonical thymine T, molecules of thymine are inserted opposite the adenine in rare tautomeric forms A₂^{*} and A₄^{*}; (c) molecules of thymine are inserted opposite molecules of adenine, molecules of adenine are inserted opposite molecules of thymine. Mutations do not form.

Suppose that after some, possibly, a long time, near the *cis-syn* cyclobutane dimer TT, another damage appears that can stop DNA synthesis. It can be caused, for example, by free radicals, the main cause of spontaneous mutagenesis. In Figure 5, it is indicated as Sp. In this case, the synthesis will continue to be carried out using error-free DNA and a sliding clamp. Let us assume that in this case the control over the formation of pyrimidine-purine bases pairs only will remain. Therefore, opposite thymine T₃^{*}, with some probability, guanine can be incorporated (Figure 5b). This will lead to the formation of untargeted delayed transition T-A → C-G (Figure 5c). For the same reasons, cytosine will be inserted opposite adenine in the A₂^{*} rare tautomeric form (Figure 5b). This will lead to the formation of untargeted delayed A-T → G-C transition (Figure 5c).

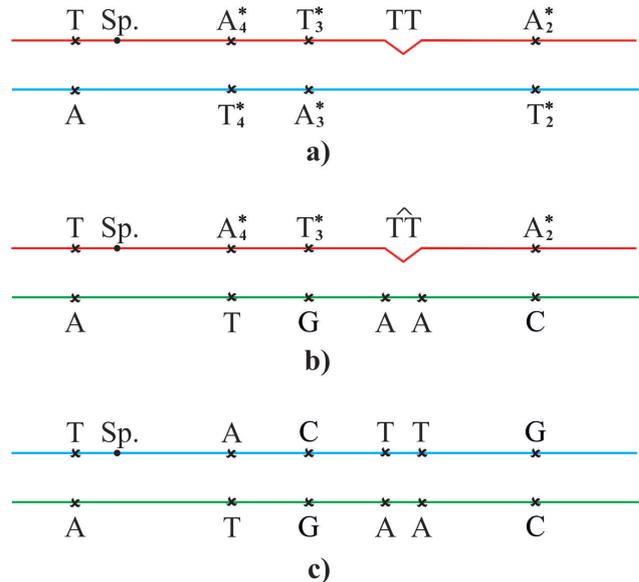


Figure 5. Error-prone or SOS-replication of the DNA containing canonical thymine, thymine in rare tautomeric form T₃^{*}, molecules of adenine in rare tautomeric forms A₂^{*} and A₄^{*} located in a small neighborhood of the *cis-syn* cyclobutane thymine dimer TT and damage Sp. capable of stopping the synthesis of DNA. Thymine T₃^{*} result in untargeted T-A → C-G transition, adenine A₂^{*} result in untargeted A-T → G-C transition, adenine A₄^{*} do not result in mutations

Note: (a) a DNA site containing canonical thymine, thymine in rare tautomeric form T₃^{*}, molecules of adenine in rare tautomeric forms A₂^{*} and A₄^{*} located in a small neighborhood of the *cis-syn* cyclobutane thymine dimer TT and damage Sp. capable of stopping the synthesis of DNA; (b) a guanine is inserted opposite thymine T₃^{*}, a cytosine is inserted opposite adenine A₂^{*}, a thymine is inserted opposite adenine A₄^{*}, molecules of adenine are inserted opposite molecules of canonical thymine T; (c) complementary base pairing occurs.

Let, after some time, many other damages appear near to the dimer TT. They can be caused by free radicals and some other chemicals (Ch.)^[114]. Synthesis will be carried out using some specialized DNA polymerases and a sliding clamp. Then transitions and transversions can be formed.

Canonical cytosine can be incorporated opposite thymine T₃^{*} (Figure 6b) and untargeted delayed T-A → G-C transversion form. The insertion of a canonical thymine opposite thymine T₃^{*} (Figure 6b) produces untargeted delayed homologous T-A → A-T transversion.

For the same reasons, guanine can be inserted opposite adenine A₂^{*} (Figure 6b). This will lead to the formation of a untargeted delayed A-T → C-G transversion (Figure 6c). In addition, opposite A₂^{*}, adenine can be inserted (Figure 6b), which results in the formation of a untargeted delayed A-T → T-A transversion (Figure 6c). Guanine can be inserted opposite adenine A₄^{*} (Figure 6b). This will lead to the formation of a untargeted delayed A-T → C-G

transversion (Figure 6c).

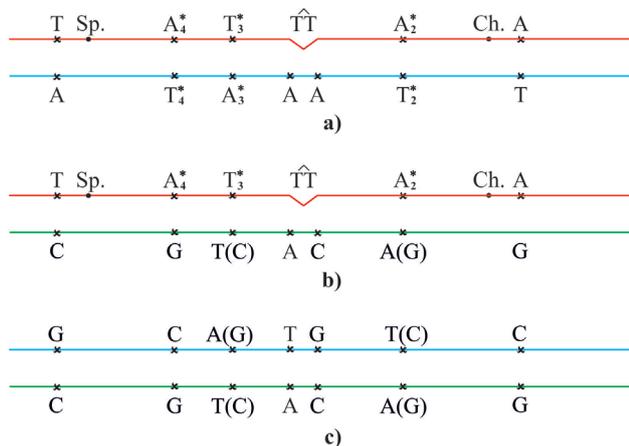


Figure 6. Error-prone or SOS-replication of the DNA containing canonical thymine, thymine in rare tautomeric form T₃^{*}, molecules of adenine in rare tautomeric forms A₂^{*} and A₄^{*} located in a small neighborhood of the *cis-syn* cyclobutane thymine dimer TT and damages Ch. and Sp. capable of stopping the synthesis of DNA. Thymine T₃^{*} result in untargeted transversion T-A→G-C or untargeted homologous transversion T-A→A-T, adenine A₂^{*} result in untargeted transversion A-T→C-G or untargeted homologous transversion A-T→T-A, adenine A₄^{*} result in untargeted transversion A-T→C-G, canonical thymine result in untargeted transversion T-A→G-C

Note: (a) a DNA site containing canonical thymine, thymine in rare tautomeric form T₃^{*}, molecules of adenine in rare tautomeric forms A₂^{*} and A₄^{*} located in a small neighborhood of the *cis-syn* cyclobutane thymine dimer TT and damages Ch. and Sp. capable of stopping the synthesis of DNA; (b) a canonical cytosine or canonical thymine is inserted opposite thymine T₃^{*}, a guanine or adenine is inserted opposite adenine A₄^{*}, a cytosine is inserted opposite canonical thymine; (c) complementary base pairing occurs.

4. Polymerase-tautomeric Model for Untargeted Delayed Base Substitution Mutations during Error-prone or SOS Synthesis of Double-stranded DNA Containing Thymine and Adenine Molecules in Canonical Tautomeric Forms

Let's see if, under certain conditions, canonical thymine and adenine result in untargeted delayed mutations. This is a very important issue, since DNA molecules are usually made up of canonical bases, and damaged bases are quite rare. Of course, thymine can form a pair with adenine (Figure 3a). The thymine cannot form hydrogen bonds with guanine or thymine. But the thymine can form hydrogen bonds with the cytosine (Figure 3c). Of course, the adenine can form a pair with the thymine (Figure 3a). In addition, canonical adenine can form hydrogen bonds with canonical guanine (Figure 3d). These facts have long

been known.

If there is only one cyclobutane pyrimidine dimer (Figure 4a) or one cyclobutane pyrimidine dimer and DNA damage caused by free radicals (Figure 5a), then adenine will be inserted opposite thymine T, and canonical thymine will be inserted opposite canonical adenine (Figure 4b, 5b). Mutations do not form (Figures 4c, 5c). And so many DNA replication cycles can go on.

Suppose that after some, possibly a long time, several other cyclobutane pyrimidine dimers were formed near the *cis-syn* cyclobutane dimer TT (Figure 5a). In this case specialized or modified DNA polymerase replicated past a *cis-syn* cyclobutane cytosine dimer with less accuracy. Let us assume that in this case the accuracy of control over the number of hydrogen bonds formed between the DNA bases will decrease. But control over the formation of pyrimidine-purine base pairs will continue. And in this case, adenine will be inserted opposite the canonical thymine (Figure 5b) and canonical thymine will be inserted opposite the canonical adenine and mutations will not form (Figure 5c).

Assume that after some time after DNA irradiation with ultraviolet light, near the canonical *cis-sin* cyclobutane thymine dimer TT, many other damages capable of stopping the DNA synthesis appear. Some of them can be caused, for example, by free radicals, the main cause of spontaneous mutagenesis. In Figure 6, I marked them as Sp. In addition, it may be other DNA damage that may be due to the action of some other chemicals that can damage the DNA. It can be heavy metals or other substances that can damage a DNA molecule. They were experimentally detected in patients with cardiovascular and cancer diseases^[114]. In Figure 6, I marked them as Ch.

As shown by experiments, if there is a large amount of DNA damage, DNA polymerases with lower speed and accuracy are involved in the translesion synthesis. In the case DNA polymerases replicated past cyclobutane dimers and other damages are highly error-prone. Most likely, specialized DNA polymerase will be pressed by a sliding clamp. Only in this case transversions can form. Cytosine may be inserted opposite thymine T (Figure 6b). In this case, transversion A-T→C-G will appear (Figure 6c). Canonical guanine may be inserted opposite canonical adenine. In this case, transversion A-T→C-G will appear (Figure 6c).

5. The Nature of Untargeted Delayed base Substitution Mutations

It can be concluded that thymine molecules in the rare

tautomeric form T_3^* , which can form hydrogen bonds with both adenine and other canonical DNA bases, can be the source of untargeted delayed base substitution mutations. Adenine molecules A_2^* and A_4^* , which can form hydrogen bonds with thymine and other canonical DNA bases, can also be the source of untargeted delayed base substitution mutations. Canonical thymine and adenine can also lead to untargeted delayed base substitution mutations. Whether or not an untargeted delayed base substitution mutation appears, is completely dependent on the neighboring environment.

If next to the thymine T_3^* or the adenine in the rare tautomeric form A_2^* or A_4^* there are no other DNA damages or there are very few of them, then synthesis through the damage will proceed quite accurately and no mutations will form. If next to the thymine in the rare tautomeric form T_3^* or the adenine in the rare tautomeric form A_2^* or A_4^* there are other lesions that can stop DNA synthesis, then the synthesis will be carried out using specialized DNA polymerases with low accuracy of synthesis. DNA synthesis can also occur with the help of constitutive DNA polymerases, but provided that they are pressed with a sliding clip. As a result, the thymine T_3^* , can cause untargeted delayed T-A→C-G transition.

And, if near the thymine T_3^* or the adenine in the rare tautomeric form A_2^* or A_4^* there will be many damages that can stop DNA synthesis, specialized DNA polymerases with very low accuracy will be involved in the translesion synthesis. In addition, their accuracy can be reduced by the operation of a sliding clamp. Thymine T_3^* can lead to an untargeted delayed T-A→G-C transversion or an untargeted delayed homologous T-A→A-T transversion. The adenine A_2^* can lead to the untargeted delayed A-T→C-G transversion and untargeted delayed homologous A-T→T-A transversion. The adenine A_4^* can lead to the formation of an untargeted delayed A-T→C-G transversion.

If there is a lot of damage on the DNA site that can stop DNA synthesis, then the thymine molecule in the canonical tautomeric form can lead to the T-A→G-C transversion only, and the adenine canonical tautomeric molecule can lead to the A-T→C-G transversion only.

6. Contribution of untargeted delayed base substitution mutations to cancer risk

Typically, mutations that lead to cancer are divided into mutations caused by hereditary factors and caused by environmental factors. Tomasetti and Vogelstein^[112] suggested that there is a third source of mutations,

these mutations appear as a result of random errors that occur during normal DNA replication. In Ref.^[112], it was concluded that only a third of cancer risk among tissues is associated with environmental factors or inherited predispositions. But basically, the risk of malignant tumors is due to random mutations that occur during normal DNA replication. In other words, according to the cancer risk model^[112], the formation of about 67% of all mutations is not caused by exposure to any mutagens. The authors conclude that no cancer prevention measures can affect this part of mutagenesis^[112].

In the currently accepted polymerase paradigm of mutagenesis, it is believed that targeted mutations appear opposite to damage that can stop DNA synthesis^[6,7,21-25]. It is believed that untargeted mutations form on non-damaged DNA sites^[6,8-13]. The nature of untargeted mutations is not understood^[3,20,43,44]. The nature of delayed mutations is not known^[3,45]. Therefore, according to the polymerase paradigm, only some of all mutations can form opposite to lesions that can stop DNA synthesis. Therefore, the conclusions of Tomasetti and Vogelstein^[112], in principle, do not contradict the generally accepted polymerase paradigm of mutagenesis. In order to test the hypothesis of Tomasetti and Vogelstein^[112], we compare the conclusions drawn in this cancer risk model with some experimental data on studies of untargeted delayed mutations.

More than half of delayed mutations are base substitution mutations^[88]. Experiments show that when combined with 8-methoxy-psoralen and long-wave ultraviolet light, about 90% of the induced mutations were untargeted delayed mutations^[113]. As shown in this paper, untargeted delayed mutations appear opposite DNA bases in certain rare tautomeric forms. These rare tautomeric forms of DNA bases can appear only under the influence of some external factors, for example, exposure to a DNA molecule with ultraviolet light or some chemicals. Moreover, these rare tautomeric forms will be stable only under certain conditions. They will be preserved only when the DNA strand opposite the corresponding bases is bent so that the hydrogen bonds between the bases are lengthened or torn. Then the hydrogen atoms will not be able to return to their previous positions. A number of studies have shown that the DNA strand bends opposite cyclobutane pyrimidine dimers^[78-82].

Therefore, in order for untargeted delayed mutations to form, several independent DNA lesions are necessary. Firstly, the action of a substance is necessary, which will lead to strong forced vibrations of the bases bonded by hydrogen bonds, which can lead to a change in the position

of one or more hydrogen atoms^[57]. Secondly, an action is needed that will lead to another DNA damage that will cause the DNA strand to bend^[26]. But this is not enough. Thirdly, it is necessary that other DNA damages appear nearby, which will lead to the induction of an error-prone or SOS system^[65]. In other words, it is necessary that DNA synthesis proceeds using specialized DNA polymerases, characterized by low accuracy of synthesis. Such damage can be formed under the influence of free radicals that appear in the processes of metabolism or other chemicals. These can be heavy metals or other substances that have been found in patients with cardiovascular and cancer diseases^[114].

We see that, at least with regard to untargeted delayed mutations when they are formed when combined with 8-methoxy-psoralen and long-wave ultraviolet light, the hypothesis of Tomasetti and Vogelstein^[112] that about 67% of all mutations are formed not caused by exposure to any mutagens, does not withstand any criticism. As the experiment shows, in this case under combined do with 8-methoxy-psoralen and long-wave ultraviolet light about 90% of the induced mutations were untargeted delayed mutations^[113]. And as the polymerase-tautomeric model shows, in order to form such mutations, the formation of several independent DNA lesions is necessary. Moreover, part of these lesions should lead to very significant effects, namely, will cause the DNA strand to bend and the induction of specialized DNA polymerases. In experiment^[113], long-wave ultraviolet light can lead to a change in the tautomeric states of DNA bases, and 8-methoxy-psoralen molecules can lead to bending of the DNA strand and induce an error-prone or SOS system.

As shown in this paper, under certain conditions, even canonical thymine or adenine can lead to mutations. This is possible when many different DNA lesions are formed, which causes not only the induction of specialized DNA polymerases, but also the work of a sliding clamp, it presses specialized DNA polymerases to template DNA, resulting in a large number of mutations.

For the untargeted delayed mutations formation, the appearance of several DNA damage is necessary. In fact, for the untargeted delayed mutations formation, significantly more DNA damage is required than with the formation of targeted mutations. Therefore, the assumption made in the cancer risk model^[112] that the formation of about 67% of all mutations is not caused by exposure to any mutagens is erroneous, at least with respect to untargeted delayed base substitution mutations. In addition, the cancer risk model^[112] contradicts the experimental data obtained in Ref.^[113].

The authors of the cancer risk model^[112] conclude that no cancer prevention measures can affect this part of mutagenesis. This conclusion, in my opinion, is also not true. I believe that for cancer patients it's not at all hopeless, as the authors of the work^[112] try to assure us. The strategy is pretty obvious. It is necessary to find out in what form heavy metals and other substances that we received with air, water and food are. A method must be developed for their removal and removal. As soon as we reduce the mutagenic and damaging load on DNA molecules, it is quite possible the body will cope with the tumor. Maybe, you may need help to ensure that all body systems work.

7. Conclusion

At present, mechanism of delayed mutations formation is not clear^[3]. In polymerase model it is assumed that sometimes DNA polymerases are inserted opposite the matrix bases, for example, those included in the composition of cyclobutane pyrimidine dimers, such canonical bases that cannot form hydrogen bonds with the matrix bases^[24]. I have proposed and are developing models for targeted^[26,31,33,38-42,52-57,115], untargeted^[58-62], and delayed mutagenesis^[32,52,62-66]. In this paper, I propose a mechanism for untargeted delayed base substitution mutations formation caused by thymine and adenine molecules. Untargeted delayed mutations are mutations that can appear after several cycles of replication after exposure to the mutagen on the so-called not damaged DNA sites. Thymine and adenine can form five rare tautomeric forms that are stable if the corresponding nucleotides are part of cyclobutane dimers or are located in small neighborhoods from them.

Error-prone and SOS synthesis of a DNA site, one strand of which contains one canonical *cis-syn* cyclobutane thymine dimer TT, and in a small vicinity of it there is thymine in the T₃* rare tautomeric form, adenine molecules in A₂* and A₄* rare tautomeric forms, as well as canonical thymine and canonical adenine. Opposite thymine T₃*, adenine can be incorporated, but may be inserted any other canonical base. Opposite adenine in rare tautomeric form of A₂*, thymine can be incorporated, but guanine or adenine may be inserted. Opposite adenine A₄* thymine can be incorporated, but guanine may be inserted.

If next to thymine T₃*, adenine A₂* or A₄* there are no other DNA damages or there are a few of them, then synthesis through the damage will proceed quite accurately and mutations will not form.

If in the small neighborhood of the thymine in the rare tautomeric form T₃* or the adenine in the rare tautomeric

form A_2^* or A_4^* there are other damages that can stop DNA synthesis, then the synthesis will be carried out using specialized DNA polymerases with low synthesis accuracy. DNA synthesis can also occur with the help of constitutive DNA polymerases, but provided that they are pressed with a sliding clamp. As a result, the thymine in the rare tautomeric form T_3^* can cause an untargeted delayed T-A→C-G transition, and the adenine molecules A_2^* or A_4^* will not lead to a mutation.

If in the small neighborhood of the thymine in the rare tautomeric form T_3^* or the adenine in the rare tautomeric form A_2^* or A_4^* , specialized DNA polymerases with very low accuracy of synthesis will be involved in the synthesis through damage. Moreover, their accuracy may be reduced by the operation of a sliding clamp. In this case, the thymine in the rare tautomeric form T_3^* can cause T-A→C-G untargeted delayed transition, and can lead to T-A→G-C untargeted delayed transversion or T-A→A-T untargeted delayed homologous transversion. The adenine in the rare tautomeric form of A_2^* can lead to the formation of untargeted delayed A-T→C-G transversion and untargeted delayed A-T→T-A homologous transversion. The adenine A_4^* can lead to the formation of an untargeted delayed A-T→C-G transversion.

The thymine in canonical tautomeric form can lead to untargeted delayed T-A→G-C transversion only, and the adenine in canonical tautomeric form can lead to untargeted delayed A-T→C-G transversion only.

It is concluded that thymine in the T_3^* rare tautomeric form, which can form hydrogen bonds with both adenine and other canonical DNA bases, can be the source of untargeted delayed base substitution mutations. In addition, adenine molecules in the rare tautomeric forms A_2^* and A_4^* , which can form hydrogen bonds with thymine and other canonical DNA bases, can also be a source of untargeted delayed base substitution mutations. In addition, thymine and adenine in canonical tautomeric forms can also lead to untargeted delayed base substitution mutations. Whether or not untargeted delayed base substitution mutation appears, is completely dependent on the neighboring environment. Not all of these damage must be mutagenic. If these lesions are able to stop DNA synthesis, then, therefore, they can lead to synthesis through damage, cause DNA polymerase with low synthesis accuracy and, therefore, contribute to mutagenesis.

As shown earlier, the formation of five rare tautomeric forms of thymines or adenines is possible. If they are located in a small vicinity of the cyclobutane pyrimidine dimer or other damage causing the DNA strand to bend, then these rare tautomeric states will be stable. Each of these bases in rare tautomeric forms can lead to certain

types of untargeted mutations. Thus, thymine T_1^* , T_4^* and T_5^* and adenine in the rare tautomeric form A_1^* can cause untargeted base substitution mutations^[32,52,60,61] only. Thymine T_2^* can lead to untargeted frameshift mutations only, for example, to untargeted insertions^[32,62]. Thymine in the T_3^* rare tautomeric form can cause untargeted delayed base substitution mutations only. The thymine in the T_3^* rare tautomeric form can cause T-A→C-G untargeted delayed transition, T-A→G-C untargeted delayed transversion or T-A→A-T untargeted delayed homologous transversion. The adenine in the A_2^* rare tautomeric form can lead to the formation of untargeted delayed A-T→C-G transversion and untargeted delayed A-T→T-A homologous transversion. The adenine in the A_4^* rare tautomeric form can lead to the untargeted delayed A-T→C-G transversion. The canonical thymine can lead to untargeted delayed T-A→G-C transversion only, and the adenine in canonical tautomeric form can lead to untargeted delayed A-T→C-G transversion only.

I developed models for targeted base substitution mutations^[26,32,33,52,55,66], targeted insertions^[32,33,39,66], targeted deletions^[32,33,40,41,66], targeted complex insertions^[32,33,42,66], delayed targeted base substitution mutations^[63,64-66]. I developed models for untargeted mutations^[32, 58-62,66] such as untargeted insertions^[32,62], untargeted base substitution mutations^[32,58-61,66] that appear immediately after irradiation, and untargeted delayed base substitution mutations. The polymerase-tautomeric models of radiation-induced genomic instability^[32,52,63-66] are able to explain such phenomena of radiation-induced genome instability as targeted delayed insertions^[32,62,66], targeted delayed base substitution mutations^[32,52,63,64,66] and untargeted delayed base substitution mutations.

Experimental studies^[27,28] provides strong support for the ideas of Watson and Crick^[30] and the polymerase-tautomeric models for mutagenesis through direct structural evidence. Thus it is need to change the paradigm in mutagenesis.

The source of untargeted delayed base substitution mutations is thymine in the T_3^* rare tautomeric form and adenine in the A_2^* and A_4^* rare tautomeric forms. But even if such DNA damage appears, in most cases they will not lead to the appearance of mutations. In order for untargeted delayed mutations to form, it is necessary that there be other DNA damage. Opposite some lesions, the DNA strand must be bent, while other lesions should be able to stop DNA synthesis.

Since, under the combined action of 8-methoxy-psoralen and long-wave ultraviolet light, about 90% of the induced mutations were untargeted delayed mutations^[113], in this case, with the onset of cancer, at least 90% of the mutations

were formed as a result of DNA damage. Long-wave ultraviolet caused the appearance of bases in rare tautomeric forms, and 8-methoxy-psoralen led to a curvature of the DNA strand and, as a result, stabilization of these rare tautomeric forms of DNA bases. In addition, 8-methoxy-psoralen led to induction of error-prone or SOS system.

Therefore, the conclusion drawn from the cancer risk model ^[112] that the formation of about 67% of all mutations is not caused by exposure to any mutagens, but is the result of normal replication, is erroneous. As we can see from the example of the untargeted delayed mutations formation, all these mutations can appear during the induction of error prone or SOS systems only. Moreover, the synthesis should occur using specialized DNA polymerases, and even the work of a sliding clamp. This is only possible when the synthesis of DNA containing a lot of damage occurs. Therefore, the conclusion of the cancer risk model ^[112] that the formation of 67% of all mutations is not caused by exposure to any mutagens, but occurs during normal DNA replication, is erroneous. It contradicts experimental facts. Naturally, the conclusion of the cancer risk model ^[112] that no cancer prevention methods can prevent 67% of all mutations is certainly wrong.

The authors of the cancer risk model ^[112] conclude that no cancer prevention measures can affect this part of mutagenesis. This conclusion, in my opinion, is also not true. I believe that for cancer patients it's not at all hopeless, as the authors of the work ^[112] try to assure us. The strategy is pretty obvious. It is necessary to find out in what form heavy metals and other substances that we received with air, water and food are. A method must be developed for their removal and removal. As soon as we reduce the mutagenic and damaging load on DNA molecules, it is quite possible the body will cope with the tumor. Maybe, you may need help to ensure that all body systems work. I hope that a deeper understanding of the mechanisms of mutations formation, and, consequently, a deeper understanding of the mechanisms of cancer formation, will allow us to develop more effective methods for the prevention and treatment of cancer.

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