

# 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

## Abstract

A polymerase-tautomer model for ultraviolet mutagenesis is described that is based on formation of rare tautomeric bases in *cis-syn* cyclobutane pyrimidine dimers. The model is based on that fact that during error-prone and SOS synthesis the induced DNA polymerase inserts canonical bases opposite the dimers in a complementary way in contrast to an complementary one in the conventional models. There are same types of potential mutagens damages in *cis-syn* cyclobutane cytosine dimers. They correspond to 7 basic types of rare tautomeric conformations of cytosine. Error-prone and SOS replication of double-stranded DNA having *cis-syn* cyclobutane cytosine dimers, with one or both bases in 4 basic types of rare tautomeric conformations of cytosine (the dimers  $CC_1^*$ ,  $CC_2^*$ ,  $CC_5^*$  and  $CC_6^*$ , with the \*indicating a rare tautomeric base and subscript referring to the particular conformation), results only in targeted substitution mutations. The structural analysis indicates that three types of *cis-syn* cyclobutane cytosine dimer containing a single tautomeric base (the dimers  $CC_1^*$ ,  $CC_2^*$ ,  $CC_5^*$ ) can cause G: C→A: T transition or G: C→C: G homologous transversion. Another two dimers ( $CC_5^*$  and  $CC_6^*$ ) can result only in G: C→T: A transversion. The dimer  $CC_6^*$  can cause G: C→A: T transition, G: C→C: G homologous transversion or G: C→T: A transversion. If both bases in the dimer are in a rare tautomeric form, then tandem mutations can be formed. The 90 substitution mutations have been interpreted from the point of view of polymerase-tautomer model of UV mutagenesis.

**Keywords:** uv-mutagenesis, rare tautomeric forms, targeted transitions, targeted transversions, *cis-syn* cytosine cyclobutane dimers, error-prone replication, sos replication

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## Some features and models of the mutagenesis

### Features of UV mutagenesis

Nearly the 48 agents were already known to induce somatic-cell mutations.<sup>1</sup> They result in cancer, aging, diabetes, and other chronic diseases.<sup>2</sup> Exposure of male mice to genotoxic agents can increase mutation frequencies in their unexposed descendants. This phenomenon, known as transgenerational genomic instability, can persist for several generations. However, little is known about the underlying mechanism.<sup>3</sup> Delayed mutations and untargeted mutations are two features of genomic instability.<sup>4,5</sup> In recent decades untargeted and delayed mutations are combined in bystander effects.<sup>6-9</sup> The bystander effect is defined as the induction of cellular damage in un irradiated cells, induced by irradiated cells in the surrounding area.<sup>7</sup> There are now known to be many late expressed effects of exposure that cannot simply be explained on the basis of direct ionizing radiation DNA damages. Examples include genomic instability, bystander effects and adaptive responses.<sup>6-9</sup>

As to understand the mechanisms of the untargeted and delayed mutations formation you first need to understand the mechanisms of the targeted base substitutions, deletions, insertions, and complex frame shift mutations. In order to understand the mechanisms of mutations formation by various mutagens, you first need to develop a model of these mechanisms caused by any one specific mutagen. Ultraviolet mutagen is understood better than anyone. So it is need to understand

of mechanisms formation of different mutations that appear when DNA molecule is irradiated with UV light.

Ultraviolet (UV) radiation produces cyclobutane pyrimidine dimers and pyrimidine-pyrimidone (6-4) photoproduct from (78% to 84%),<sup>10,11</sup> hydrated bases (1%-7%) (cytosine bases form more often), linked DNA-protein and DNA-DNA, and break in filaments (less than 1%) in *Escherichia coli*<sup>12,13</sup> yeast,<sup>14</sup> in xeroderma pigmentosum variant cell extracts and in mammalian cells under induced by UVB irradiation.<sup>15</sup> In addition to pyrimidine-pyrimidine adducts, the purines-pyrimidine adducts are formed, for example, in consecution TpA, but they form very rarely.<sup>16</sup> *Cis-syn* cyclobutane pyrimidine dimers account for a large majority of UV-induced mutations.<sup>17,18</sup> If not all dimers are moved cyclobutane pyrimidine dimers<sup>19-22</sup> and pyrimidine-pyrimidone (6-4) photoproduct<sup>23,24</sup> may produce mutations. Replication past the *cis-syn* T-C cyclobutane dimer, like replication past its T-T and U-U counterparts, is in fact >95% accurate and that the frequencies of bypass are also very similar for these photoproducts.<sup>25</sup> Overall, 5 - 12% of cyclobutane dimers and (6-4) adduct result in replication errors.<sup>26</sup> *Cis-syn* cyclobutane pyrimidine dimers constitute a much more important premutagenic lesion than (6-4) pyrimidine-pyrimidone photoproducts, and it has been estimated that *cis-syn* cyclobutane pyrimidine dimers account for ≈80% of UV-induced mutations in mammalian cells.<sup>15</sup> In addition to the formation of cyclobutane dimers at TT sites, UV induces the formation of cyclobutane dimers at 5'-TC-3' and 5'-CC-3' dipyrimidine sites, and both in yeast and humans, UV-

induced mutations occur predominantly by a C-to-T transition at the 3' base.<sup>27-29</sup> Usually mutations occur opposite the photoproducts during error-prone and SOS replication, repair or transcription.<sup>19,25,30-36</sup> Such mutagenesis is termed targeted.<sup>37,38</sup> Sometimes mutations are formed in the vicinity of the damage, a process that is termed untargeted mutagenesis.<sup>39,40</sup> Sometimes delayed mutations are formed.<sup>41-44</sup> Untargeted and delayed mutations are two features of genomic instability.<sup>5</sup> Cyclobutane pyrimidine dimers and (6-4) photoproducts cause substitution mutations (transitions and transversions),<sup>25,45,46</sup> frame shift mutations (deletions and insertions)<sup>39,47-49</sup> and complex frame shift mutations.<sup>50,51</sup> Mismatch-repair systems suppress only about half of UV mutations.<sup>52</sup> Delayed mutation and untargeted mutations are two features of genomic instability.<sup>5</sup> Sunlight ultraviolet irradiation has been implicated in the etiology of human skin cancer.<sup>53</sup> As a rule sewed DNA-protein and DNA-DNA and break in filaments result only in frame shift mutations. Cytosine dimers more often result in mutations than thymine dimers. Hot spots of UV-mutagenesis are sites consisting of photoproducts having thymine and cytosine bases or two cytosine bases.<sup>27,28</sup>

### DNA polymerases involved in SOS synthesis of DNA

As a rule, DNA synthesis is a highly accurate process. If an erroneous base is inserted during the replication process, it is usually removed by 3'→5' exonuclease activity.<sup>54,55</sup> UV irradiation generates cyclobutane dimers and 6-4 adducts in DNA, which if not removed by excision repair, result in the induction of the error-prone or SOS system. Error-prone or SOS induction allows DNA synthesis to occur even on templates containing cyclobutane dimers and 6-4 adducts,<sup>56</sup> replication on a damaged DNA template, however, results in mutations. Specialized mutagenic DNA polymerases *E. Coli* poll II, poll IV, and poll V are capable of replicating past DNA lesions, a process called translation synthesis.<sup>57-59</sup> Lesion bypass during *in vitro* replication of duplex DNA containing *cis-syn* cyclobutane thymine dimers occurs by translation synthesis.<sup>60</sup> Translation replication is carried out by specialized DNA polymerases.<sup>61</sup> Mutations arise when modified by sliding clamp<sup>62,63</sup> or specialized low fidelity<sup>62,64-74</sup> DNA polymerases are involved in DNA synthesis. There is a cooperative and sequential assembly of translation synthesis polymerases in response to DNA damage.<sup>75</sup>

Poll IV and Poll V polymerases of the *Escherichia coli* are inducible components of the SOS system.<sup>39,76-79</sup> They have low-fidelity DNA polymerase activity.<sup>80</sup> Poll IV and Poll V appear to extend mismatched base pairs efficiently in the absence of other proteins. Polymerase Poll V catalyses template-directed nucleotide incorporation. Poll IV produces untargeted mutations.<sup>39,78</sup> Poll V, in contrast to Poll III, does not possess any associated proof-reading functions.<sup>76,77</sup> This mutator activity is influenced by the defective proof-reading sub-unit of Poll III.<sup>79, 81</sup>

DNA polymerase poll V is responsible for most of the mutagenesis associated with the SOS response.<sup>82, 83</sup> *Escherichia coli* DNA polymerase V bypasses *cis-syn*-cyclobutane thymine-thymine dimer and TT (6-4)-photoproduct, especially TT (6-4)-photoproduct, in an error-prone manner.<sup>74</sup> DNA polymerase poll V bypasses T-T *cis-syn* cyclobutane dimers *in vitro* and *in vivo*.<sup>74,84-86</sup> Very little replication past a T-T *cis-syn* cyclobutane dimer normally takes place in *Escherichia coli* in the absence of DNA polymerase V.

### DNA polymerases involved in error-prone synthesis of DNA

Poll η and Poll ζ polymerases of the yeast are inducible components of the error-prone system.<sup>65-68</sup> In the case of yeast Poll ζ is highly error-

prone.<sup>65,66,70,71,87</sup> DNA polymerase ζ replicated past a thymine-thymine *cis-syn* cyclobutane dimer.<sup>68</sup> DNA polymerase ζ is responsible for insertion in bypass of and a basic site, T-T (6-4) photo adduct and T-T *cis-syn* cyclobutane dimer events other than those in which polymerase η performs this function.<sup>68</sup> The Poll ζ translation synthesis DNA polymerase is responsible for over 50% of spontaneous mutagenesis and virtually all damage-induced mutagenesis in yeast.<sup>88</sup> Poll ζ catalyzes nucleotide incorporation opposite AAF-guanine and TT (6-4) photoproduct with a limited efficiency. Secondly, more efficient bypass of these lesions may require nucleotide incorporation by other DNA polymerases followed by extension DNA synthesis by Poll ζ.<sup>89</sup>

DNA polymerase η was found to be involved only rarely in the bypass of the T-T (6-4) photo adduct or the a basic sites in the sequence context used, although, as expected, it was solely responsible for the bypass of the T-T *cis-syn* cyclobutane dimer.<sup>68</sup> The human DNA polymerase pollη bypasses *cis-syn*-cyclobutane thymine-thymine dimer efficiently in a mostly error-free manner but does not bypass TT (6-4)-photoproduct.<sup>90</sup> *Drosophila* DNA polymerase pollη efficiently bypass a *cis-syn* cyclobutane thymine-thymine dimer in a mostly error-free manner. *Drosophila* DNA polymerases pollη shows limited ability to bypass a (6-4)-photoproduct at thymine-thymine (6-4)-photoproduct or at thymine-cytosine (6-4)-photoproduct in an error-prone manner.<sup>90</sup> Pollη plays the protective role of against UV-induced lesions and the activation by UV of pollη-independent mutagenic processes.<sup>91</sup> Although accessory proteins clearly participate in pollη functions *in vivo*, they do not appear to help suppress UV mutagenesis by improving pollη bypass fidelity per se.<sup>92</sup> The yeast DNA polymerase η bypasses a *cis-syn* cyclobutane pyrimidine dimers and (6-4) photoproducts efficiently and accurately.<sup>93</sup> DNA polymerase η plays an important *in vivo* role in inserting G opposite the 3' T of 6-4 TT photoproducts.<sup>94</sup>

DNA polymerase has been implicated in translation DNA synthesis of oxidative and UV-induced lesions. *Drosophila* DNA polymerase pollI efficiently bypass a *cis-syn* cyclobutane thymine-thymine dimer in a mostly error-free manner.<sup>89</sup> Purified human PollI responded to a template TT (6-4) photoproduct by inserting predominantly an A opposite the 3' T of the lesion before aborting DNA synthesis. In contrast, human Poll was largely unresponsive to a template TT *cis-syn* cyclobutane dimer.<sup>95</sup> In cells lacking Poll is responsible for the high frequency and abnormal spectrum of UV-induced mutations, and ultimately their malignant transformation.<sup>73</sup> The mutagenic properties of a lesion can depend strongly on the particular enzyme employed in bypass.<sup>84</sup> Human DNA polymerase κ (Pollκ) is unable to insert nucleotides opposite the 3'T of a *cis-syn* T-T dimer, but it can efficiently extend from a nucleotide inserted opposite the 3'T of the dimer by another DNA polymerase.<sup>96</sup> Human mitochondrial DNA polymerase pollγ mis incorporated a guanine residue opposite the 3'-thymine of the dimer only 4-fold less efficiently than it incorporated an adenine.<sup>72</sup> De Marini<sup>97</sup> shown that different mutagens induce the same primary class of base substitution and frameshift mutations in most organisms, this reflecting the conserved nature of DNA replication and repair processes.

### Sliding clamp in mutagenesis

DNA polymerase III (Poll III) plays the main role in SOS replication in bacterial cells.<sup>81,98</sup> UV-induced mutagenesis has been studied extensively in *E. Coli*, and several *E. Coli* DNA-polymerases involved in the process have been identified. Most erroneously

incorporated nucleotides are removed during DNA replication by 3'→5' exonuclease, which are components of DNA-polymerases I and II, or by autonomous 3' 5' exonuclease (subunit  $\epsilon$  of DNA-polymerase III).<sup>81</sup> The possessiveness factor, i.e., subunit  $\beta$ , plays a decisive role in controlling the ratio between the polymerase and proofreading activities of DNA-polymerase III.<sup>99</sup> Its molecules form a ring-like moving platform or a "sliding clamp" that contains a central hole for double-stranded DNA to pass through as the polymerase moves along the DNA. It positions DNA-polymerase III on the template and ensures the highly processive synthesis of DNA.<sup>100</sup> Even when an erroneous base pair is formed, the sliding clamp mechanism presses the DNA polymerase against the template and prevents the 3'→5'-exonuclease from removing the "improper" base, this result in mutations.

DNA polymerases  $\delta$  (Poll $\delta$ ) and  $\epsilon$  (Poll $\epsilon$ ) play the main role in error-prone replication in eukaryotic cells.<sup>101,102</sup> Mammalian proliferating cell nuclear antigen (PCNA) is the processivity factor in sliding clamp for essential eukaryotic DNA polymerases  $\delta$  and  $\epsilon$ . The trimetric PCNA ring is striking similar to the dimeric ring formed by the  $\beta$  subunit (processivity factor) of the essential *Escherichia coli* DNA polymerase III holoenzyme and the gene 45 protein of T4 phage.<sup>99,103</sup> Even when an erroneous base pair is formed, the sliding clamp mechanism presses the DNA polymerase against the template and prevents the 3'→5'-exonuclease from removing the "improper" base, this result in mutations. Cyclobutane pyrimidine dimers are responsible for most of the PCNA ubiquitination events after UV-irradiation.<sup>104</sup>

Sliding clamps are used by numerous different DNA polymerases and repair proteins in both prokaryotic ( $\beta$  clamp)<sup>105</sup> and eukaryotic (PCNA clamp) organisms.<sup>106</sup> Sliding  $\beta$  clamps functions with Poll I, Poll III holoenzyme and with the three damage inducible polymerases Poll II, Poll IV, and Poll V.<sup>62,74</sup> During DNA damage, a damaged base on the leading strand will halt fork progression by the Poll III. A low-fidelity polymerase like Poll IV and Poll V presumably trade places with the stalled Poll III on  $\beta$  for lesion bypass, after which the Poll III may resume synthesis.<sup>107,108</sup> DNA polymerases Poll III, Poll IV and Poll V increase cell fitness.<sup>109</sup> The  $\beta$  sliding clamp of *E. Coli* binds two different DNA polymerases at the same time. One is the high-fidelity Poll III chromosomal replicas and the other is Poll IV or Poll II polymerase.<sup>107,110</sup>

When the error-prone or SOS system is induced, control over the templating of bases becomes weaker, and bases are inserted opposite dimers. Even when an erroneous base pair is formed, the "sliding clamp" mechanism presses the DNA-polymerase against the template and prevents the 3'→5' exonuclease from removing the "improper" base. Alternatively, synthesis is performed by DNA polymerases having no exonuclease at all (e.g., *E. Coli* DNA polymerase IV or V, or DNA polymerase Poll $\zeta$ , Poll $\eta$  or Poll $\kappa$ ).

### DNA polymerase incorporates canonical bases capable of forming hydrogen bonds with cyclobutane pyrimidine dimers in template DNA

The efficiency and fidelity of nucleotide incorporation by high-fidelity replicative DNA polymerases are governed by the geometric constraints imposed upon the nascent base pair by the active site. Kinetic analyses of nucleotide incorporation opposite a *cis-syn* cyclobutane thymine-thymine dimer and an identical nondamaged sequence by yeast DNA polymerase  $\eta$  (Poll $\eta$ ) strongly support a mechanism in which the nucleotide is directly inserted opposite the *cis-syn* cyclobutane thymine-thymine dimer by using its intrinsic base-

pairing ability without any hindrance from the distorted geometry of the lesion.<sup>66</sup> Both a human polymerase  $\kappa$  (Poll $\kappa$ ) and polymerase  $\eta$  rely on Watson-Crick hydrogen bonding. A low-fidelity polymerase  $\eta$  shows more of a dependence upon Watson-Crick hydrogen bonding than does human Poll $\kappa$ , which differs from Poll $\eta$  in having a higher fidelity.<sup>111</sup> These and other results support conclusion that during the error prone or SOS synthesis, the canonical bases, which can form hydrogen bonds with bases of the template DNA, are incorporated opposite cyclobutane pyrimidine dimers.<sup>112</sup>

### Models of mutagenesis

**Polymerase paradigm of mutagenesis:** At present, the conventional paradigm relates the reason of mutations exclusively to sporadic errors of DNA polymerases.<sup>74,82,83,113,114</sup> Bresler<sup>113</sup> proposed a mechanism for the formation of base-substitution mutations during the synthesis of DNA containing cyclobutane pyrimidine dimers. He assumed that the mutations arise because the DNA-polymerase sometimes incorporates non complementary nucleotides opposite the cyclobutane pyrimidine dimers. From the point of view of mutagenesis, this model assumes that, for example, all the cyclobutane thymine dimers are identical, and that mutations are induced by errors produced by DNA-polymerases when using DNA containing dimers as a template. However the approach resting exclusively on the polymerase paradigm is limited, it contradicts several experimental facts and can't explain some mutagenesis phenomena.<sup>112</sup>

The reasons of mutation origination are explained by the so-called "*A-rule*".<sup>113,116</sup> The experiment shows that adenine (A) is most frequently incorporated opposite T (*cis-syn*) T dimers (94%), guanine (G) - opposite T (*cis-syn*) C dimers (95%).<sup>25,26,66,68, 74,93,116-118</sup> Poll V incorporates adenine opposite T (*cis-syn*) T dimers (98%).<sup>74</sup> Poll $\eta$  incorporates adenine opposite T (*cis-syn*) C dimers (99%) and guanine (G) opposite T (*cis-syn*) C dimers.<sup>46,66,73,117,118</sup> Poll $\eta$  incorporates guanine opposite T (*cis-syn*) C.<sup>93</sup> Polymerase *exo-T7* DNA poll incorporates adenine opposite T (*cis-syn*) T dimers (98%).<sup>116</sup> Polymerases poll $\eta$  and poll V incorporates adenine opposite 3'-T TT.<sup>93,119</sup> *In vitro* replication studies of Poll $\eta$  show that it replicates past 5'-T-T3' and 5'-T-U3' cyclobutane pyrimidine dimers, incorporating G or T nucleotides opposite the 3' nucleotide.<sup>73</sup> Poll $\eta$  incorporates G opposite the 3' T or (6-4) adducts.<sup>94</sup> Cyclobutane pyrimidine dimers as well as, to a lesser extent, the thymine-thymine pyrimidine-pyrimidone (6-4) photo product, were bypassed. Poll  $\beta$  mostly incorporates the correct dATP opposite the 3'-terminus of both cyclobutane pyrimidine dimers CPD and the (6-4) photoproduct but canals misinsert Dctp.<sup>120</sup> Purified yeast Poll $\zeta$  performed limited translation synthesis opposite a template TT (6-4) photoproduct, incorporating A or T with similar efficiencies (and less frequently G) opposite the 3' T, and predominantly A opposite the 5' T.<sup>89</sup> DNA Poll $\zeta$ , essential for UV induced mutagenesis, efficiently extends from the G residue inserted opposite the 3' T of the (6-4) TT lesion by Poll $\eta$ , and Poll $\zeta$  inserts the correct nucleotide A opposite the 5' T of the lesion.<sup>118</sup> These biochemical observations are in concert with genetic studies in yeast indicating that mutations occur predominantly at the 3' T of the (6-4) TT photoproduct and that these mutations frequently exhibit a 3' T→C change that would result from the insertion of a G opposite the 3' T of the (6-4) TT lesion. It has been shown that a cytosine or an adenine is the predominant nucleotide inserted opposite abasic sites.<sup>121</sup> Basing on polymerase paradigm Taylor conclude that "the instructional or non-instructional behavior of a lesion in directing nucleotide insertion is not an invariant property of the lesion, but depends on the structure and mechanism of the polymerase involved".<sup>82</sup>

These models undoubtedly describe some cases and features of mutagenesis. In *E. Coli*, DNA polymerases IV and V, as a rule, function when DNA polymerase III has a defective  $\epsilon$  subunit.<sup>63,81,108</sup> However, the majority of mutations occur when DNA polymerase III has fully functional 3'→5' exonuclease proofreading activity (a fully functional  $\epsilon$  subunit), when the SOS system is induced, and when the "sliding clamp" mechanism is operating.<sup>56,59</sup> Hence, this generally accepted paradigm describes only a small part of mutagenesis in *E. coli*. Moreover, this approach ignores the structure of the DNA damage.

**Tautomeric model of mutagenesis:** In the paper by Watson and Crick<sup>122</sup> it was stated that the spontaneous mutagenesis is based on capability of nucleotide bases to change their tautomeric state, which influences the character of base pairing. The participation of rare tautomeric forms in mutagenesis was repeatedly discussed.<sup>123–125</sup> The role of tautomeric transitions in mutagenesis of the analogues of the bases is almost universally recognized.<sup>126</sup> The mutagenesis models resting on rare tautomer hypothesis are, in fact, physical-chemical. Usually, they are simply stating that a change in the tautomeric state of bases is possible and concluding an erroneous pairing and, consequently, base substitution mutation to result from that change. The biological data are, as a rule, ignored. Spontaneous mutagenesis models suppose that the tautomeric state of DNA bases can be changed due to thermal vibrations. However, such bases in rare tautomeric forms will, most likely, be effectively removed by repair systems. The operation of free radicals formed in metabolism processes is known to be the main cause of spontaneous mutagenesis. These free radicals give damages of bases, sugar-phosphate stoma, etc.<sup>127,128</sup> The removal of DNA structure damages by repair systems and conditions for them to be a template for DNA synthesis, etc, are not usually examined. Wang et al. provides structural evidence for the rare tautomer hypothesis of spontaneous mutagenesis.<sup>129</sup>

There are now two practically independent approaches to explaining mutagenesis. Physicists and chemists consider polymerases to be important; however, they largely ignore their role in the process and rely almost exclusively upon Watson and Crick's paradigm.<sup>123,130,131</sup> In contrast, most biologists cite Watson and Crick's idea, but base their research on the polymerase paradigm.<sup>74,82,83,113,114</sup>

**Bystander Effects:** Bystander effects include untargeted and delays mutations.<sup>6–9</sup> Naga Saw and little first reported bystander effects.<sup>132</sup> It is believed now that untargeted and part of delayed mutations appears on not damaged DNA sites.<sup>5</sup> These, so called, untargeted effects are demonstrated in cells that are the descendants of irradiated cells either directly or via media transfer (radiation-induced genomic instability) or in cells that have communicated with irradiated cells (radiation-induced bystander effects).<sup>133</sup> The dogma that genetic alterations are restricted to directly irradiated cells has been challenged by observations in which effects of ionizing radiation, characteristically associated with the consequences of energy deposition in the cell nucleus, arise in non-irradiated cells. These, so called, untargeted effects are demonstrated in cells that have received damaging signals produced by irradiated cells (radiation-induced bystander effects) or that are the descendants of irradiated cells (radiation-induced genomic instability).<sup>134</sup>

The most convincing explanation of radiation-induced genomic instability attributes it to an irreversible regulatory change in the dynamic interaction network of the cellular gene products, as a response to non-specific molecular damage.<sup>135</sup> The central role of

cell-cell communication on non-targeted effects is underlined.<sup>136</sup> The discovery of non-targeted and delayed radiation effects has challenged the classical paradigm of radiobiology.<sup>137</sup> It is assumed that a radiation cancer-causing target is protein.<sup>138</sup> Furthermore, it is still not known what the initial target and early interactions in cells are that give rise to non-targeted responses in neighboring or descendant cells.<sup>6</sup> Moreover, it was concluded that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions. The majority is due to "bad luck," that is, random mutations arising during DNA replication in normal, noncancerous stem cells.<sup>139</sup>

**Deamination of cytosine in mutagenesis:** Cytosine easily undergoes hydrolytic Deamination.<sup>140</sup> One hypothesis is that UV-induced mutations occur only after deamination of the cytosine or 5-methylcytosine within the pyrimidine dimer.<sup>141</sup> Two models have been proposed: "error-free" bypass of deaminated cytosine-containing cyclobutane pyrimidine dimers by DNA polymerase  $\eta$ , and error-prone bypass of cyclobutane pyrimidine dimers and other UV-induced photo lesions by combinations of translation DNA synthesis and replicative DNA polymerases the latter model has also been known as the two-step model, in which the cooperation of two (or more) DNA polymerases as misinserters and (mis)extenders is assumed.<sup>142</sup> Sunlight-induced cytosine to thymine mutation hotspots in skin cancers occur primarily at methylated CpG sites that coincide with sites of UV-induced cyclobutane pyrimidine dimer formation. The cytosine or 5-methyl-cytosine in cyclobutane pyrimidine dimers are not stable and deaminate to uracil and thymine, respectively, which leads to the insertion of adenine by DNA polymerase  $\eta$  and defines a probable mechanism for the origin of UV-induced cytosine to thymine mutations.<sup>143, 144</sup> There is evidence to suggest that, depending on solvent polarity, a cytosine or a 5-methylcytosine in a *cis-syn* cyclobutane pyrimidine dimer can adopt three tautomeric forms, one of which could code as thymine.<sup>145</sup> 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 for this to be significant in *Escherichia coli*.<sup>25</sup>

**Polymerase-tautomeric model for ultraviolet mutagenesis:** I have attempted to Construct a polymerase-tautomeric model for UV-induced mutagenesis,<sup>112,146–163</sup> based on idea by Watson and Crick<sup>122</sup> that changes in tautomeric state are possible for DNA bases. A mechanism for changes in the tautomeric state of base pairs has been proposed.<sup>146,152,161–163</sup> It was assumed that the tautomeric state of the constituent bases may change during the formation of cyclobutane pyrimidine dimers.<sup>112,146,152</sup> 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.<sup>149,151</sup> Five new rare tautomeric conformations of the adenine and thymine<sup>150,152</sup> and seven of the cytosine and guanine<sup>146</sup> are proposed that are capable of influencing the character of base pairing. It is shown that such rare tautomeric forms of DNA bases are stable when they are parts of the *cis-syn* cyclobutane pyrimidine dimers and they are stable under DNA synthesis.<sup>112</sup>

*Cis-syn* cyclobutane thymine dimers wherein a thymine occurs in the rare tautomeric forms  $T_1^*$ ,  $T_4^*$ , or  $T_5^*$  were shown to cause targeted base substitution mutations only.<sup>112,149</sup> *Cis-syn* cyclobutane thymine dimers wherein a thymine is in the rare tautomeric form  $T_2^*$  may result in targeted frame shift mutations (targeted insertions and targeted deletions).<sup>156,157</sup> I propose the mechanisms of targeted

insertions formation during error-prone or SOS synthesis of DNA containing *cis-syn* cyclobutane cytosine<sup>155</sup> and thymine<sup>156</sup> dimers. A mechanism was proposed for targeted complex insertions<sup>158</sup> and targeted deletions<sup>157,159</sup> caused by *cis-syn* cyclobutane thymine dimers. *Cis-syn* cyclobutane thymine dimers wherein a thymine is in the rare tautomeric form  $T_3^*$  may result in targeted delayed base substitution mutations.<sup>160</sup> Polymerase-tautomeric model for untargeted substitution mutations formation when DNA molecule contains *cis-syn* cyclobutane thymine dimers also have been developed.<sup>148, 151, 154</sup> A polymerase-tautomeric model was developed for the formation of hot and cold spots of UV-induced mutagenesis.<sup>153</sup>

## Development of a polymerase-tautomeric model for targeted substitution mutations at *cis-syn* cyclobutane cytosine dimers

### Mechanism of alteration of DNA bases tautomeric state under *cis-syn* cytosine dimers formation

I use the polymerase-tautomer model for ultraviolet mutagenesis to determine which targeted mutations form by the error-prone or SOS replication opposite *cis-syn* cyclobutane cytosine dimers. The polymerase-tautomer model for ultraviolet mutagenesis is based on formation of rare tautomeric bases in *cis-syn* cyclobutane pyrimidine dimers. It was found that cytosine, guanine and other nucleic acid bases primarily exist in the form of two tautomer canonic and hydroxo forms with a possible small presence of the amino tautomeric form.<sup>124,125,164</sup> The existence of up to four tautomers of guanine, namely enol- $N_7H$ , keto- $N_7H$ , keto- $N_9H$  and enol- $N_9H$  in the gas phase has been suggested.<sup>123,165</sup> The double-proton transfer in adenine-thymine and guanine-cytosine base pairs at room temperature in gas phase and with the inclusion of environmental effects has been investigated.<sup>166,167</sup> It was shown that double-proton transfer results in stable rare tautomeric forms only in guanine-cytosine base pairs.<sup>166,168,169</sup>

As known, there are four types of cyclobutane pyrimidine dimers: *Cis-syn*, *Trans-syn*, *Cis-anti* and *Trans-anti* dimers.<sup>170</sup> This analysis only considers the *cis-syn* cyclobutane dimer, which is the most common type. There is no change in the orientation of the bases relative to the sugar-phosphate backbone as a result of *cis-syn* cyclobutane dimer formation.<sup>170</sup> The mechanism of changes in tautomeric states is a radiation less deexcitation of the quantum of UV energy.<sup>112,152</sup> In result the hydrogen atom in hydrogen bond can assume new positions.<sup>112,146,150,152</sup> It was shown what under *cis-syn* cyclobutane pyrimidine dimers formations the tautomer states of bases can change. A mechanism of changes in the tautomeric state of base pairs for the case when DNA molecule is UV-irradiated and *cis-syn* cyclobutane pyrimidine dimers are formed.<sup>112,146,150,152</sup> As quantum-mechanical calculations show hydrogen atoms return in original position.<sup>166,168,169</sup> Only one of new positions can be stable.<sup>166,168,169</sup>

Assume that all processes of energy spreading are complete and that the UV-quantum is localized to one of the bases. This results in the excitation of electronic-vibration states.<sup>171</sup> There are three channels for the relaxation of electronic-vibration states. First is fractional energy transfer to neighboring bases with radiation of some of the energy.<sup>172,173</sup> This is the most probable process for the relaxation of a single electronic level,<sup>174</sup> and it results in undamaged DNA. For a triplet level excitation, the most probable process for relaxation involves the transformation of energy to oscillations of the neighboring atoms.<sup>174</sup> It is known<sup>172,173</sup> that non radiative deexcitation in DNA molecules occurs in a small volume of 3-5 bases pairs. This

results in a strong "local heating-up", followed by initiation of normal oscillations of the bases. After several oscillations, taking  $\sim 10^{-14}$  -  $10^{-12}$  sec,<sup>175,176</sup> the vibratory system will reach equilibrium.

The oscillations of atoms will cause changes in the distances between the paired bases, in other words, in the lengths of H-bonds. For pairs of bases and in model systems, the first excited state results in a decrease in the height of potential energy barriers for proton transfer among H-bonds.<sup>177</sup> For example, the barriers are lowered by a factor of approximately 1.5 for the H-bond of a 7-azaindole dimer.<sup>177</sup> Such change of proton potential occurs in  $\sim 10^{-16}$  sec and results in an increased probability that the hydrogen atom is in an excited state.<sup>178</sup> Grebneva<sup>163</sup> calculated the probabilities of a change in the lengths of H-bonds (R) for distances of  $\pm 0.01$ nm to  $\pm 0.05$ nm during several "instantaneous temperatures" of local heating-up.

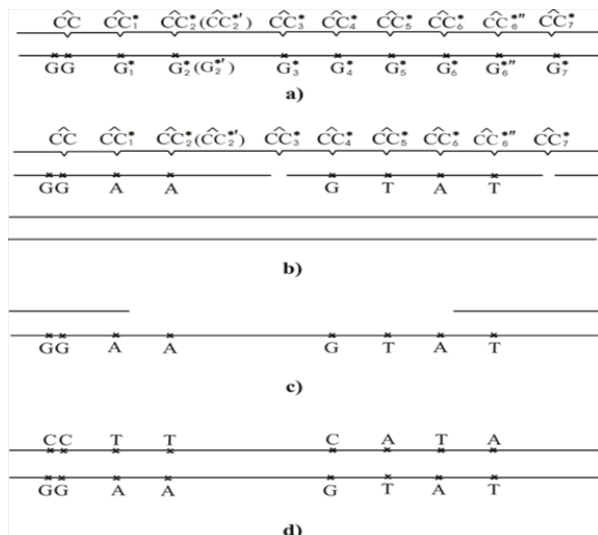
Tolpygo and Grebneva<sup>175</sup> described the shapes of the potential curves for the protons of all three H-bonds of Watson and Crick's G: C base pair for several lengths of H-bonds. It turned out that a decrease in the length of a H-bond by 0.02 nm from the equilibrium transforms the proton potential into a single-well. With an increase in H-bond length, the second minimum becomes more and more obvious. The dynamics of the changes in the shape of proton potential for a wide spectrum of H-bond lengths were calculated.<sup>179</sup> The curves were designed with a system (water dimer,  $(H_2O)_2$ ) having H-bond parameters very similar to those of the H-bonds in base pairs.<sup>179</sup> Semi-empirical potential function developed by us, has been used.<sup>180</sup>

The H-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 (R) of a valence bond changes, the length (r) changes very little. But distance from the hydrogen to the second atom (R-r) varies considerably.<sup>181</sup> A decrease in the R of a H-bond by 0.04-0.05nm sufficient to place the atom of hydrogen almost in the center of H-bond where it forms a strong bond. Therefore, when the H-bond is extended, the hydrogen atom can assume new positions. If the atoms of hydrogen participating in the formation of H-bonds are excited,<sup>178</sup> their effective radius will increase by  $\sim 0.01$  nm and there will be a higher probability that the hydrogen atom will participate in a H-bond. Second, Danilova et al.<sup>177</sup> found that potential energy barriers are reduced when the hydrogen's are in an excited state. Third, some of the new proton positions can be stable, or even favorable from the point of view of the energy compared with other potential positions.<sup>166,168,169</sup> The assumption of favorable conformations is possible, as the lifetime of a triplet state is  $\sim 10^{-6}$  sec.<sup>174</sup> The lifetime of the excited H-bond is  $\sim 4 \times 10^{-9}$  sec,<sup>182,183</sup> and the characteristic periods of atomic oscillations are  $\sim 10^{-14}$  -  $10^{-12}$  sec.<sup>175</sup> Therefore, there will be not more than several 10s of oscillations up to 100oscillations that influence the length of the H-bond. This results in a time of  $\sim 10^{-10}$  sec for any one conformation.

The proposed model is in a good agreement with the results obtained by other authors.<sup>185</sup> Light-mediated proton transfer is required for the photo chromic transformation of organic compounds.<sup>176</sup> Proton transitions in H-bonds occur in acids and bases, in crystals, proteins, molecular membranes, enzymes, and in other systems.<sup>176</sup>

Similar processes can occur upon dimer formation. The mechanism responsible for dimer formation and changes in tautomeric states is one and the same, namely, a radiation less deexcitation of the quantum of UV energy. As a consequence, changes in the tautomeric state of bases can occur upon dimer formation. Hovorun<sup>178</sup> has developed a model of semi open Meta stable states in DNA. Logically, the process

of dimer formation proceeds through a semi open metastable state, and changes in the tautomeric conformation of bases follow the induction of metastable semi open states. The rare tautomeric states of thymine and adenine,<sup>152</sup> which are represented in Figure 1, were obtained by assuming the occurrence of semi open metastable states.<sup>185</sup>



**Figure 1** G, C base pairs formed by bases in canonical and rare tautomeric conformations. (a) (G) and (C) are in canonical tautomeric forms; (b-h) guanine ( $G_i^*$ ) and cytosine ( $C_i^*$ ) are in rare tautomeric forms,  $i=1+7$ .

It was shown what under dimers formations the tautomeric states of bases can change. A mechanism of changes in the tautomeric state of base pairs for the case when DNA molecule is UV-irradiated and thymine dimers are formed is the very mechanism when cytosine dimers are formed.<sup>112,152</sup> The process of dimer formation proceeds through a semi open metastable state, and changes in the tautomeric conformation of bases follow the induction of metastable semi open states.<sup>112,152</sup>

In a canonical DNA molecule, conformational fluctuations of different DNA sites result in different metastable states. The exposure of bases from a double spiral to the solution is known as “opening” or “melting” of Watson and Crick’s pairs. In this case, the hydrogen bonds between DNA bases are broken.<sup>179</sup> Metastable states developing with incomplete opening of the pair and with partial conservation of H-bonds and with the amine group free from H-bond are called semi open metastable states.<sup>180</sup> There exist several models of semi open metastable states.<sup>180</sup> In our opinion, the model developed by Hovorun<sup>177</sup> is well-grounded; it explains a number of phenomena and is confirmed by experimental data.

To find out what new tautomeric state can be formed at cytosine dimers formation, let us address to this structural-dynamical model of DNA semi open states by Hovorun<sup>177</sup> It is rather probable that the process of tautomeric state change goes in two stages. At the first stage, the metastable semi open DNA states are formed. At the second stage, the formed rare metastable tautomeric states transform into the stable ones. Let us study possible new tautomeric states of the Watson-Crick’s pair guanine-cytosine which may influence the character of pairing. According to Hovorun model,<sup>177</sup> for guanine-cytosine pair there is several semi open states. It is well known that the lifetime of semi open states in DNA  $\sim 10^{-6}$ s.<sup>189</sup> The processes for tautomeric state change are much less durable.<sup>112,153</sup> Therefore, they may take place during the time of existence of semi open states. Figure 1 shows

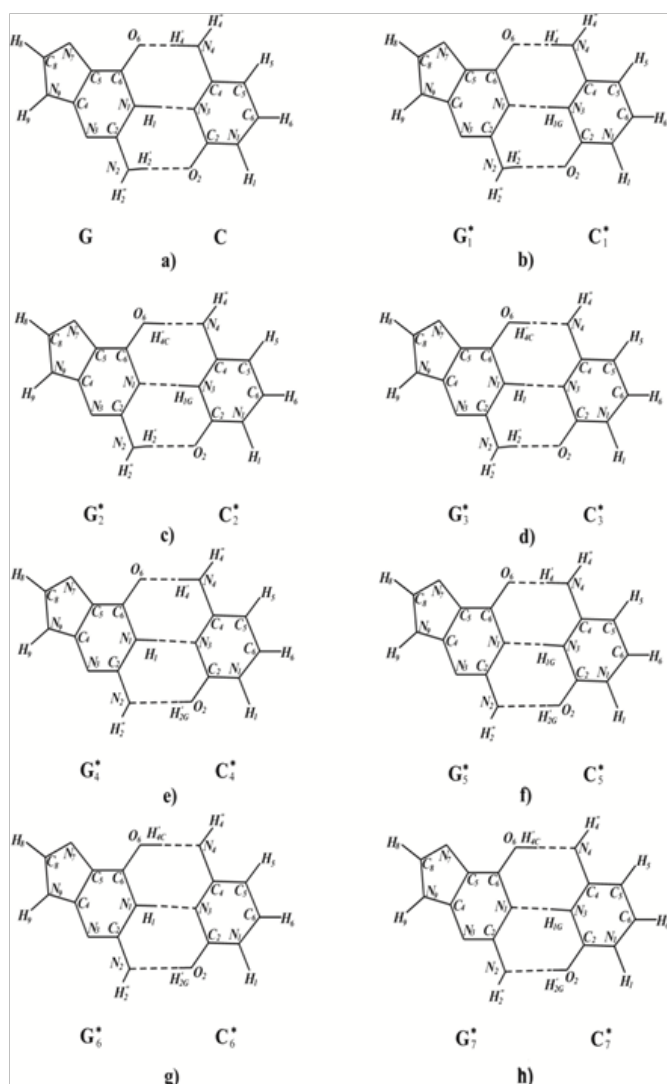
possible tautomeric states of bases of the G: C pair which could result from the processes described.

When *cis-syn* cyclobutane pyrimidine dimer is formed, the DNA strand containing this dimer becomes bent and the H-bonds become broken.<sup>181-185</sup> That’s why in double-stranded DNA the mentioned rare tautomeric states are stable. DNA synthesis is rare quick even under the SOS synthesis, while it takes comparatively much time to change tautomeric states of bases because of the interaction with water molecules. Therefore these rare tautomeric forms will be also stable during DNA molecule synthesis when the DNA molecule is for a while in single-stranded form.<sup>112</sup> The resulted were 7 rare tautomeric states of the cytosine and guanine Figure 1,<sup>146</sup> that were capable of influencing the character of base pairing. Rare tautomeric forms of various types may occur with different probabilities. In Figure 1 the pairs of bases, which are in rare tautomeric forms, are enumerated in the order corresponding to the lowering of possible probabilities of their formation. Asterisk (\*) means that the base is in a rare tautomeric form. *Cis-syn* cyclobutane cytosine dimers cause mutations more frequent than *cis-syn* cyclobutane thymine dimers.<sup>27,28</sup> The following analysis considers mechanisms for targeted base substitution mutations when the template DNA contains *cis-syn* cyclobutane cytosine dimers.

### Error-prone and SOS replication of DNA containing *Cis-Syn* cyclobutane cytosine dimers

The polymerase-tautomer model for ultraviolet mutagenesis is based on that fact that during error-prone and SOS synthesis the induced DNA polymerase inserts canonical bases opposite the dimers; the inserted bases are capable of forming hydrogen bonds with bases in the template DNA. To determine which of the canonical bases will be inserted by the error-prone or SOS inducible DNA polymerase opposite *cis-syn* cyclobutane cytosine dimers Figure 2a consider the constraints on the formation of hydrogen bonds (H-bonds) between the bases of the template DNA and the inserted bases. DNA polymerase incorporates canonical bases capable of forming hydrogen bonds with dimerized bases in template DNA.<sup>112</sup> First of all; H-bonds do not necessarily form. During error-prone or SOS synthesis of DNA containing cyclobutane pyrimidine dimers, nucleotide bases are inserted opposite the cyclobutane pyrimidine dimers without the removal of the dimer-containing sites. This only possible when the DNA polymerases, such as Poll $\delta$  and Poll $\epsilon$  of the eukaryotic cells or Poll III of the *Escherichia coli* are pressed on the DNA by the sliding clamp, obstructing the operation of exonuclease, or when the synthesis involves low-fidelity specialize DNA polymerases, such as Poll $\eta$  and Poll $\zeta$  polymerases of the yeast or Poll IV and Poll V polymerases of the *Escherichia coli*. Under these conditions, the strand of DNA containing no photo-dimers does not result in mutations Figure 2b.

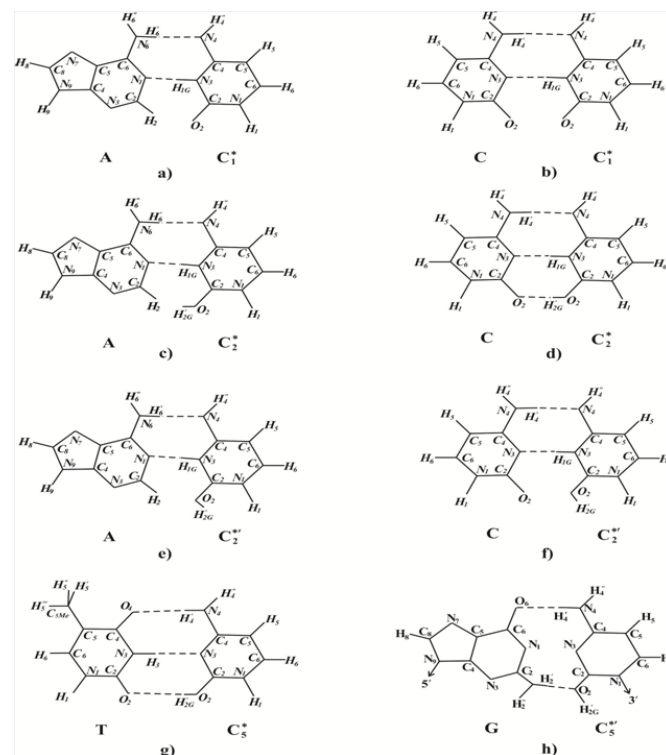
The rare  $C_1^*$  cytosine tautomer Figure 1b does not form H-bonds with canonical guanine G because of the repulsion of hydrogen  $H_I$  of guanine and  $H_{IG}$  of  $C_1^*$  cytosine atoms. Cytosine  $C_1^*$  is capable of forming two hydrogen bonds with adenine Figure 3a. The insertion of a canonical form of adenine opposite  $C_1^*$  produces G: CA:T transition Figure 2. Canonical tautomeric forms of cytosine can be incorporated opposite the rare  $C_1^*$  Figure 1b cytosine tautomer Figure 3b. In this case, homologous G: C $\rightarrow$ C: G transverse will result Figure 5. The rare  $C_1^*$  tautomer cannot form H-bonds with canonical tautomer of thymine because of the repulsion of hydrogen atoms  $H_3$  of thymine and  $H_{IG}$  of  $C_1^*$  cytosine. So, rare  $C_1^*$  cytosine may produce G:C $\rightarrow$ A:T transition and homologous G:C $\rightarrow$ C:G transverse, but cannot cause G:C $\rightarrow$ T:A transverse or form error free pair G:C $\rightarrow$ G:C.



**Figure 2** SOS replication of DNA containing cytosine dimers. (a) DNA strand (horizontal line) containing *cis-syn* pyrimidine dimers  $CC_1^*$ ,  $CC_2^*$ ,  $CC_3^*$ ,  $CC_4^*$ ,  $CC_5^*$ ,  $CC_6^*$ , and  $CC_7^*$ , where some of the cytosine molecules are in the rare tautomeric forms shown in Figure 1. The opposite DNA strand contains molecules of guanine in the conformations  $G_1^*$ ,  $G_2^*$ ,  $G_2'^*$ ,  $G_3^*$ ,  $G_4^*$ ,  $G_5^*$ ,  $G_6^*$ , and  $G_7^*$  as indicated in Figure 1; (b) DNA strand containing the dimers after replication by the modified DNA polymerase during SOS synthesis; (c) DNA site containing the dimers is cut out by the excision repair; (d) excision gap is incorporated.

The rare  $C_2^*$  cytosine tautomer Figure 1c does not form hydrogen bonds with canonical guanine G because of the repulsion of hydrogen atoms  $H_1$  of guanine and  $H_{1G}$  of  $C_2^*$  cytosine. But it can form two hydrogen bonds with canonical cytosine Figure 3d. The rare  $C_2^*$  cytosine tautomer is capable of forming two hydrogen bonds with adenine Figure 3c. Cytosine  $C_2^*$  cannot form H-bonds with canonical thymine because of the repulsion of hydrogen atoms  $H_3$  of thymine and  $H_{1G}$  of cytosine  $C_2^*$ . The insertion of a canonical form of cytosine opposite cytosine  $C_2^*$  produces homologous G:CC:G transverse Figure 5, the insertion of a canonical form of adenine opposite cytosine  $C_2^*$  produces G:C→A:T transition Figure 2. If the  $H'_{2G}$  hydrogen atom in  $C_2^*$  cytosine turns as shown in Figure 3e,  $C_2'^*$  cytosine could form H-bond with adenine Figure 3e and cytosine Figure 3f. These pairings result in G:C→A:T transition Figure 2 or homologous G:C→C:G transverse Figure

5. So, the rare  $C_2^*$  and  $C_2'^*$  cytosine tautomer may produce G:C→A:T transition and homologous G:C→C:G transverse, but cannot cause G:C→T:A transverse or form error free pair G:C→G:C.

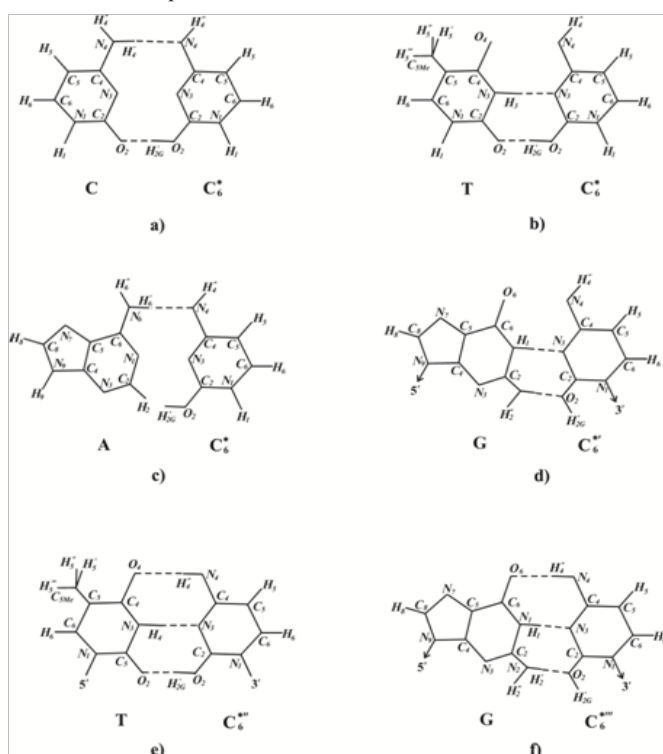


**Figure 3** Possible base pairs formed between bases in rare and canonical tautomeric conformations. (a)  $C_1^*$  and A; (b)  $C_1^*$  and C; (c)  $C_2^*$  and A; (d)  $C_2^*$  and C; (e)  $C_2^*$  and A; (f)  $C_2^*$  and C; (g)  $C_5^*$  and T; (h)  $C_5^*$  and G.

The rare  $C_5^*$  cytosine tautomer Figure 1f can't form hydrogen bonds with canonical guanine G because of the repulsion of the  $H'_{2G}$  hydrogen of the cytosine  $C_5^*$  and hydrogen  $H'_2$  of guanine G and because of the repulsion of hydrogen atoms  $H_1$  of guanine and  $H_{1G}$  of  $C_5^*$  cytosine. The rare  $C_5^*$  cytosine can't form H-bonds with canonical cytosine because of the repulsion hydrogen  $H'_4$  of the cytosine  $C_5^*$  and hydrogen  $H_4$  of the canonical cytosine. Cytosine  $C_5^*$  can't form H-bonds with adenine because of the repulsion of the hydrogen  $H'_4$  of the cytosine  $C_5^*$  and hydrogen  $H'_6$  of the canonical adenine. But  $C_5^*$  can form three H-bonds with canonical thymine Figure 3g. The insertion of a canonical form of canonical thymine opposite cytosine  $C_5^*$  produces G:C→T:A transverse Figure 5. If the  $H'_{2G}$  hydrogen atom in  $C_5^*$  cytosine turns as shown in Figure 3h,  $C_5'^*$  cytosine could form H-bond with guanine Figure 3h, it may not result in mutations. So, the rare  $C_5^*$  cytosine tautomer may produce G:C→T:A transverse, but can't cause G:C→A:T transition and homologous G:C→C:G transverse or form error free pair G:C→G:C.

The rare  $C_6^*$  cytosine tautomer Figure 1f can't form hydrogen bonds with canonical guanine G because of the repulsion of the  $H'_{2G}$  hydrogen of the cytosine  $C_6^*$  and hydrogen  $H_2$  of guanine G. The rare  $C_6^*$  cytosine tautomer Figure 1g can form two H-bonds with canonical cytosine Figure 4a, one H-bond with canonical adenine Figure 4c and two H-bonds with canonical thymine Figure 4b. Canonical tautomeric forms of cytosine, adenine or thymine can be incorporated opposite  $C_6^*$  cytosine. These insertions result in G:C→C:G homologous transverse Figure 5, G:CA:T transition Figure 2 or G:CT:A transverse Figure 5. If the  $H'_{2G}$  hydrogen atom in  $C_6^*$

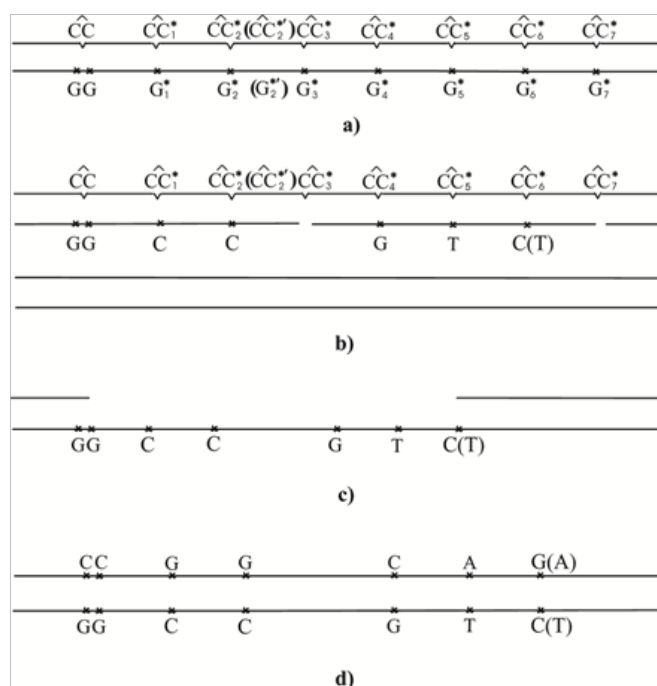
cytosine turns as shown in Figure 4d, the resulting  $C_6^{*'}$  cytosine may form two H-bonds with canonical guanine Figure 4d. However, if the  $H'_4$  hydrogen atom in  $C_6^*$  cytosine turns as shown in Figure 4e,  $C_6^{*''}$  cytosine could form three H-bonds with thymine Figure 4e. The insertion of a canonical tautomeric form of thymine opposite  $C_6^{*''}$  cytosine can produce G:C→T:A transverse Figure 2. If the  $H'_{2G}$  hydrogen atom in  $C_6^{*''}$  cytosine turns as shown in Figure 4f, the resulting  $C_6^{*'''}$  cytosine may form three H-bonds with canonical guanine Figure 4f and it may not result in mutations. So, the rare  $C_6^*$  cytosine tautomer may produce G:C→A:T transition, G:C→C:G homologous transverse and G:C→T:A transverse, but can't form error free pair G:C→G:C. The rare  $C_6^{*''}$  cytosine tautomer can produces G:C→T:A transverse, but can't cause G:C→A:T transition and homologous G:C→C:G transverse or form error free pair G:C→G:C.



**Figure 4** Possible base pairs formed between bases in rare and canonical tautomeric conformations. (a)  $C_6^*$  and C; (b)  $C_6^*$  and T; (c)  $C_6^*$  and A; (d)  $C_6^{*'}$  and G; (e)  $C_6^{*''}$  and T; (f)  $C_6^{*'''}$  and G.

The rare  $C_4^*$  cytosine tautomer can pair with guanine; it may not result in mutations. The rare  $C_3^*$  and  $C_7^*$  cytosine tautomer do not form H-bonds with any canonical tautomer. So it is possible that DNA polymerase will not incorporate any bases opposite this rare tautomer and that DNA synthesis will result in a one-nucleotide gap. Figure 2 shows the most probable bases incorporated by the modified DNA-polymerase opposite  $C_1^*$  cytosine. The  $CC_3^*$  and  $CC_7^*$  dimers will give gaps, and guanine will be likely incorporated opposite the  $CC_4^*$  dimer. Adenine will be incorporated opposite  $CC_1^*$ ,  $CC_2^*$ ,  $CC_2^{*'}$  and  $CC_6^*$  dimers. Thymine will be incorporated opposite  $CC_5^*$  and  $CC_6^{*''}$  dimers. It is known that the DNA strand having no dimers does not result in mutations Figure 2b. We shall consider that one-nucleotide gaps have been repaired, and the DNA site with dimers Figure 2b is repaired by the excision repair. Next, the DNA site having dimers is removed Figure 2c. The bases are inserted by an ordinary DNA polymerase in the excision gap Figure 2d. The complementary incorporation results in mutations: transitions G:C→A:T and transverse G:CT:A.

Figure 5 shows another variant of events development. The  $CC_3^*$  and  $CC_7^*$  dimers will give gaps as be before. The  $CC_4^*$  dimer most likely will not result in mutation. The  $CC_1^*$ ,  $CC_2^*$  and  $CC_2^{*'}$  dimers will cause the G:C→C:G homologous transverse. The  $CC_5^*$  dimer will induce G:C→T:A transverse. The  $CC_6^*$  dimer can induce G:C→T:A transverse or G:C→C:G homologous transverse. These predictions need experimental verifications.



**Figure 5** SOS replication of DNA containing cytosine dimers. (a) DNA strand (horizontal line) containing *cis-syn* pyrimidine dimers  $CC_1^*$ ,  $CC_2^*$ ,  $CC_2^{*'}$ ,  $CC_3^*$ ,  $CC_4^*$ ,  $CC_5^*$ ,  $CC_6^*$ ,  $CC_7^*$ ; (b) DNA strand containing the dimers after replication by the modified DNA polymerase during SOS synthesis. The resulting are homologous transversions G→C and transversions G→T; (c) DNA strand containing the dimers dimers is cut out by the excision repair; (d) the excision gap is incorporated. The resulting are homologous transversions G-C→C-G and transversions G-C→T-A.

## Discussion

Let us interpret some experimental data from the viewpoint of the polymerase-tautomer model of UV mutagenesis. For example let us consider big collection of mutations caused by, cytosine photoproducts and cytosine-thymine photoproducts under hot spots UV mutagenesis investigation.<sup>27,28</sup> We will investigate the UV mutational spectrum for *supF* (157G171C) variant having 90 mutations consisting of 68 G:CA:T transitions, 14 homologous transversions G:C→C:G, two G:C→T:A transversions and six tandem mutations (when both bases of a photo dimer result in mutations).<sup>27,28</sup> The CC photoproducts are sources of tandem mutations and all tandem mutations are G:C→A:T transitions. An interesting aspect of the mutations at 150 sites in the variant *supF* (157G171C) gene is that most of them were G: C→C: G transversions. This was quite different from almost all the other mutations which were G: C→A: T transitions. Homologous G: C→C: G transversions are not in accord with the “A-rule”. The polymerase-tautomer model explains these results in the following way.

Dipyrimidine photoproducts  $C_{99}C_{100}$  and  $C_{103}C_{104}$  give only transitions G: C→A:T. Dipyrimidine photoproduct  $C_{99}C_{100}$  gives two transitions G:C→A:T opposite cytosine  $C_{99}$ . So, they most likely



correspond to the most probable *cis-syn* cyclobutane dimers  $C_j^*C$ . But it is quite probable that this is less possible *cis-syn* cyclobutane dimer  $C_2^*C$  or even *cis-syn* cyclobutane dimer  $C_6^*C$ . Moreover, dipyrimidine photoproduct  $C_{99}C_{100}$  gives tandem mutation in the form of two transitions opposite cytosine  $C_{99}$  and cytosine  $C_{100}$  at a time. Then *cis-syn* cyclobutane dimer  $C_j^*C_j^*$  or, with all versions taken into account, *cis-syn* cyclobutane dimer  $C^*C^*$  ( $i=1, 2, 6; j=1, 2, 6$ ) will correspond to the above *cis-syn* cyclobutane dimer, since only cytosine's  $C_1^*, C_2^*$  and  $C_6^*$  can result in transitions G: C→A:T. *Cis-syn* cyclobutane dimer  $C_{103}C_{104}$  gives four transitions G:C→A:T opposite cytosine  $C_{104}$ . So, *cis-syn* cyclobutane dimer  $CC_i^*$  ( $i=1, 2, 6$ ) will correspond to it. Dipyrimidine photoproduct  $C_{108}C_{109}$  gives 11 transitions G: C→A:T and one transversions G:C→T:A opposite cytosine  $C_{108}$ . The 11 transitions can be given only by *cis-syn* cyclobutane dimer  $C_i^*C$  ( $i=1, 2, 6$ ), while the transverse G:C→T:A can be only due to *cis-syn* cyclobutane dimers  $C_5^*C$  and  $C_6^*C$ , since only cytosine's  $C_5^*$  and  $C_6^*$  can result in such a transverse. Dipyrimidine photoproduct  $C_{111}T_{112}$  gives one homologous transverse G: C→C:G. It can be caused only by *cis-syn* cyclobutane dimer  $C_i^*T$ , where  $i=1, 2, 6$  since only cytosine's  $C_1^*, C_2^*$  and  $C_6^*$  can result in homologous transversions G:C→C:G. Dipyrimidine photoproduct  $T_{112}C_{113}$  gives one transition G:C→A:T, consequently, it is in correspondence with *cis-syn* cyclobutane dimer  $TC_i^*$  ( $i=1, 2, 6$ ). Dipyrimidine photoproduct  $C_{124}T_{125}$  gives one transition G:C→A:T, hence *cis-syn* cyclobutane dimer  $C_i^*T$  ( $i=1, 2, 6$ ) corresponds to it.

Dipyrimidine photoproduct  $C_{129}T_{130}$  gives two transitions G: C→A:T opposite cytosine  $C_{129}$  and one transition A:T→G:C opposite thymine  $T_{130}$ . In the first case, *cis-syn* cyclobutane dimer  $C_i^*T$  ( $i=1, 2, 6$ ) corresponds to it and in the second case - dimer  $CT_j^*$  since only  $T_j^*$  can result in transition A:T→G:C.<sup>112</sup> Dipyrimidine photoproduct  $C_{133}T_{134}$  gives four transitions G: C→A: T and one transverse G:C→T:A opposite cytosine  $C_{133}$  and one transverse A:T→T:A opposite thymine  $T_{134}$ . In the first four cases, *cis-syn* cyclobutane dimer  $C_i^*T$  ( $i=1, 2, 6$ ) will correspond to it. In the fifth case-*cis-syn* cyclobutane dimer  $C_i^*T$  ( $i=5, 6$ ). In the sixth case, it will be *cis-syn* cyclobutane dimer  $CT_i^*$  ( $i=1, 5$ ), since only thymine's  $T_1^*$  and  $T_5^*$  may result in homologous transversions A: T→T: A.<sup>112</sup> Dipyrimidine photoproduct  $C_{139}T_{140}$  gives one transition G: C→A: T opposite cytosine  $C_{139}$ , consequently, there will be the correspondence with *cis-syn* cyclobutane dimer  $C_i^*T$  ( $i=1, 2, 6$ ).

Dipyrimidine photoproduct  $C_{150}T_{151}$  gives two transitions G:C→A:T and twelve homologous transversions G:C→C:G opposite cytosine  $C_{150}$ , consequently, *cis-syn* cyclobutane dimer  $C_i^*T$  ( $i=1, 2, 6$ ) will correspond to it. The larger number of transversions is, evidently, due to suppression of the enzymes responsible for the absence of pyrimidine-pyrimidine or purines - purines pairing, not due to some additional features of premutagenic lesion dimer. Dipyrimidine photoproduct  $T_{154}C_{155}$  gives six transitions G: C→A: T opposite cytosine  $C_{155}$ , so *cis-syn* cyclobutane dimer  $TC_i^*$  ( $i=1, 2, 6$ ) will correspond to it. Dipyrimidine photoproduct  $C_{156}C_{157}$  gives three transitions G: C→A:T opposite cytosine  $C_{157}$  and one tandem mutation consisting of two transitions G:C→A:T. In the first three cases there will be the correspondence with *cis-syn* cyclobutane dimer  $CC_i^*$  ( $i=1, 2, 6$ ) and in the last case with *cis-syn* cyclobutane dimer  $C_i^*C_j^*$  ( $i=1, 2, 6; j=1, 2, 6$ ). Dipyrimidine photoproduct  $C_{159}C_{160}$  gives one transition G: C→A:T opposite cytosine  $C_{159}$ , consequently, *cis-syn* cyclobutane dimer  $C_i^*C$  ( $i=1, 2, 6$ ) may correspond to it. Dipyrimidine photoproduct  $T_{162}C_{163}$  gives six transitions G: C→A: T opposite cytosine  $C_{163}$ , consequently, *cis-syn* cyclobutane dimer  $TC_i^*$  ( $i=1, 2,$

6) will correspond to it. Dipyrimidine photoproduct  $C_{164}T_{165}$  gives four transitions G: C→A: T opposite cytosine  $C_{164}$ , consequently, *cis-syn* cyclobutane dimer  $C_i^*T$  ( $i=1, 2, 6$ ) will correspond to it. Dipyrimidine photoproduct  $C_{168}C_{169}$  gives twelve transitions G: C→A: T, six ones due to cytosine  $C_{168}$  and the other six - cytosine  $C_{169}$ , so in the first case, *cis-syn* cyclobutane dimer  $C_i^*C$  ( $i=1, 2, 6$ ) will correspond to it and in the latter case - *cis-syn* cyclobutane dimer  $CC_i^*$  ( $i=1, 2, 6$ ). Dimer  $C_{172}C_{173}$  gives three transitions G: C→A: T opposite cytosine  $C_{173}$ , consequently, *cis-syn* cyclobutane dimer  $CC_i^*$  ( $i=1, 2, 6$ ) will correspond to it. Dipyrimidine photoproduct  $C_{174}C_{175}$  gives three transitions G: C→A:T opposite cytosine  $C_{174}$ , so *cis-syn* cyclobutane dimer  $C_i^*C$  ( $i=1, 2, 6$ ) will correspond to it. Besides, it gives four tandem mutations in the form of transitions G: C→A: T, consequently, in this case, *cis-syn* cyclobutane dimer  $C_i^*C_j^*$  ( $i=1, 2, 6; j=1, 2, 6$ ) will correspond to it.

So, the polymerase-tautomer model may explain all 90 substitution mutations. The most frequently arising transitions G: C→A:T and homologous transversions G:C→C:G may correspond the most probable rare  $C_j^*$  tautomeric forms of cytosine and two G:C→T:A transversions may correspond less probable rare  $C_5^*$  or  $C_6^*$  tautomeric form of cytosine. Predominance of homologous transversions G: C→C:G causing by dipyrimidine photoproduct  $C_{150}T_{151}$  has naturally explanation since cytosine  $C_1^*, C_2^*$ , and  $C_6^*$  may cause homologous transversions G:C→C:G.

## Conclusion

The polymerase-tautomer model for ultraviolet mutagenesis is described that is based on formation of rare tautomeric bases in *cis-syn* cyclobutane pyrimidine dimers. The model is based on that fact that during error-prone and SOS synthesis the induced DNA polymerase inserts canonical bases opposite the dimers; the inserted bases are capable of forming hydrogen bonds with bases in the template DNA. Error-prone and SOS replication of double-stranded DNA having *cis-syn* cyclobutane cytosine dimers, with one or both bases in a rare tautomeric conformation, results in targeted transitions and transversions. There are same types of potential mutagens damages in *cis-syn* cyclobutane cytosine dimers. They correspond to 7 fundamental types of rare tautomeric conformations of cytosine.

The structural analysis indicates that three types of *cis-syn* cyclobutane cytosine dimer containing a single tautomeric base (the *cis-syn* cyclobutane cytosine dimers  $CC_1^*, CC_2^*, CC_2^{*'}$ ) can cause G: C→A:T transition and G:C→C:G homologous transverse. Another two *cis-syn* cyclobutane cytosine dimers (the dimers  $CC_5^*$  and  $CC_6^{*'}$ ) can result only in G: C→T: A transverse. The *cis-syn* cyclobutane cytosine dimer  $CC_6^*$  can cause G: C→A:T transition, G:C→C:G homologous transverse or G:C→T:A transverse. The 90 substitution mutations are formed in the hot spots of UV mutagenesis<sup>27, 28</sup> are interpreted from point in view polymerase-tautomer model. The polymerase-tautomer model may explain all 90 targeted base substitution mutations. The polymerase-tautomeric model is able to explain the mechanisms formation of targeted base substitution mutations, targeted insertions, targeted deletions and targeted complex insertion, and hot and cold spots of UV-induced mutagenesis. The polymerase-tautomeric model for bystander effects is able to explain the mechanisms formation for untargeted substitution mutations and targeted.

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## Conflict of interest

Author declares that there is no conflict of interest.

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