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The sources of spontaneous mutations could include DNA bases tautomerism

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Based on the data on activation of many molecular processes during cell functioning under different conditions the multitudinous sources of spontaneous mutations are briefly summarized. The mechanisms of different class mutation emergence as well as possible mechanisms regulating mutation rates are characterized. As the level of dNTP pool is significantly elevated in genotoxically stressed cells, leading to an increased number of mutations appearing, it is proposed that this effect could be accounted for DNA bases tautomerism occurring in tight molecular space overcrowded with dNTP. The mutation rate could be controlled by regulating the dNTP concentration.

Keywords: spontaneous mutagenesis, DNA bases tautomerism, level of intracellular of dNTP.

When John W. Drake who edited *Genetics* for a long period of time decided to stop this activity, special issue of this journal was prepared to honor him with the collection of papers on mutation and repair as a field in which he played the central role [1-8]. This happened in 1998. Since then mutation remains a goal of intense study as a factor changing genetic information, driving force of evolution and a tool in establishing species barriers due to genetic divergence emerged at the account of accumulation of multiple mutations [9].

Mutation is commonly defined as occasional changes in the sequence of nucleotides [10], and though a deeper insight to define mutation waits for its time currently there is a suggestion "to ignore biophysical and biochemical aspects…and adopt a simple transmission genetic approach, concerned with inputs, outputs and rates" [11].

The study of spontaneous mutations, the rates of their arising and the way to harness them is not only of heuristic importance but also of practical value. Thus, wonder-drug Gleevec as an inhibitor of hybrid kinase functioning in chronic myeloid leukemia cells became known because of a breakthrough in cancer medication. However, soon resistance to this drug emerged due to spontaneous mutations arisen that made the drug ineffective [12].

The focus of this short review is summary of the known sources of endogenous spontaneous mutations and discussion on the possibility of insertion into DNA chains of the rare non-canonic base pairs such as A:C and G:T. As quantum-mechanical analysis showed [13] these could be formed due to proton ability to migrate from one to another atom in a base molecule that gives rise to tautomer molecules. They influence the fidelity of the replicative enzyme function, the wrong nucleotide could be inserted leading if avoided editing and mismatch repair to mutation emergence. If H-bonding

may be non-crucial for base selection by DNA polymerase and molecule geometry is the most important [14], the question arises if and how proton tautomer transition could influence geometry of a base.

On the sources of endogenous spontaneous mutations. The data of their study till 1998 are reviewed in [15] and shown at the Fig 1.

First, these sources could be divided into two groups. One of them includes mutations resulting from selection of a wrong nucleotide and other errors in the replicative process especially vulnerable at the template places containing homopolymeric tracts and some high-ordered structures. Here insertions and deletions could most probably occur. Probably because DNA polymerase can make mistakes it was endowed with the editing ability and the study of mechanisms and conditions of this activity opens the possibility of controlling spontaneous mutation rates.

The other group includes mutations originating at the background of activity of genes comprising the systems of genetic repair. First of all this is mismatch repair – MMR system. Genes of this system are described in species from bacteria to man.

They could correct not only mismatches but also deletions/insertions [16], though some "labor division" is observed.

The special repair system is nucleotide excision repair-NER [17], studied with the aid of *rad* mutants highly sensible to UV light. Recently it was shown that for this repair the translesion DNA polymerase responsible for introduction of mutations non-repaired with MMR genes is required [18].

The well-known system of genetic repair is repair of DNA double-stranded breaks (DSB) involving recombination between DNA molecules [19-21]. This could occur both error-free and error-prone. Once yeast site-specific endonuclease HO cuts the genome and the cell viability depends on repair involving recombination and translesion polymerases the yield of mutations becomes 100-fold higher [16]. But in G2 of cell cycle when an intact sister chromatid is available, DSB repair is possible due to homologous error-free recombination. If DSB occurs in G1 haploid cell, the only possibility that could save the cell is error-prone joining of non-homologous ends-NHEJ. Recently it has been shown that a special *Xlf1* gene was needed for this joining due to the formation of a ligase complex [22]. This reparation recruits Ku antigen capable of binding to broken ends independently of sequence context [23, 24].

Different exogenous and endogenous DNA damages may destroy bases so that sites that lack purine or pyrimidine (so called AP sites) may appear in a DNA molecule. Repair of such defects was dubbed base excision repair-BER. This repair is fulfilled due to the activity of special enzymes such as AP-endonuclease/3'diestherase encoded by *APN1* gene and DNA glycosylases (gene encoding uracil-DNA-glycosylase *UNG1* is known). Effects of these genes activity in BER processes are described in [16].

We omit here characterization of mutations resulting from mobile elements transposition events because a special review of this issue is dedicated to this source of spontaneous mutations.

The advent of genomic and post genomic era in biology shed bright light to the study on genome organization and functioning in different organisms. The latest achievements in this field are summarized in the book [25]. (The book is reviewed in [26]). Characterization of different structural elements of genome, peculiarities of their activation is accompanied by analysis of the processes leading to mutation emergence both as programmed and non-programmed evens. They determine the level of spontaneous mutagenesis observed in the normal and pathological state. The book shows that the rate of mutations appearance may differ 1000-fold for different parts of the genome. This depends on mutating target position in genome, its functional role, chromosomal context, the character of nucleotide sequence, and selective recruitment to appropriate cis-elements of special trans-elements. Also, important is the time of the target replication in cell cycle. Moreover, this rate depends on how intense the process is and how the participants of this process are chemically modified under the available conditions of cell functioning. Fig. 2 shows these sources of spontaneous mutagenesis as "kinetic" and "epigenetic" mutagenesis respectively.

At present it is known that a higher level of transcription is accompanied by a higher number of mutations (TAM-transcription activated mutagenesis). Promoter inactivation leads to disappearance of the nearest

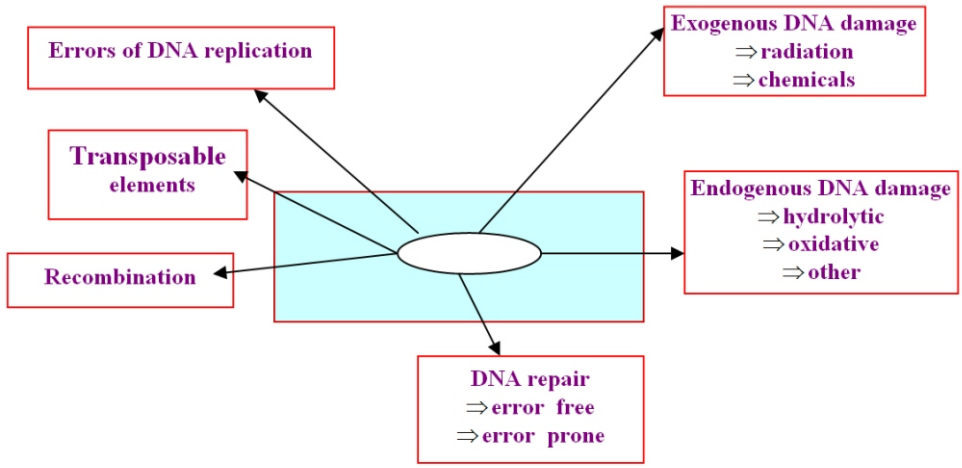

Fig.1 Possible sources of spontaneous mutations [15]

hot spot. Number of mutations grows if sites binding transcriptional factors are damaged. Substitutions are better fixed in non-translatable part of mRNA for non-conservative proteins and much less in case of conservative proteins/

As for epigenetic mutagenesis it was shown that DNA hypomethylation leads to increasing the number of mutations. The vast majority of them are the result of 5mC deamination. Clarification of the role of epigenetic changes made an attractive idea that cancer may be the result of alterations in the pattern of epigenetic marking of genes in stem and progenitor cells and that leads to DNA damage [27].

On the mechanisms of mutation induction. This is a long studied field and B.Lewin summarized the results obtained in a series of books [28]. Here we shortly mention about AID and Apobec enzymes called "mutagenases" that are widely reviewed [25, 27]. These enzymes are endowed with the ability to deaminate cytosine converting it to uracil. This finally leads to mutation emergence as G:C A:T transition. The enzymes function as a tool to create genetic diversity where it is necessary (for example to provide antibody diversity in recognizing an astronomic number of antigens [29, 30]).

Different classes of DNA polymerases were discovered (reviewed in [31]) and the question arose of their destination in cell functioning. It was noticed that a damaged template could be involved into replication but with a less precision. Such a synthesis was called translesion synthesis-TLS [32]. Study of SOS repair in bacteria [33] led to identification of a gene *Umu C* that served as a polymerase functioning with a low precision [34, 35]. The enzyme could guard the cell viability successfully though many mutations emerged. Another traslesion polymerase Din B (polV) was discovered [36]. It specifically senses the defects of G in the genome always inserting C. The enzyme may be important for eukaryotes too, especially if the status of revealed CarG box is essential for gene regulation [37] and also for sensing 8-oxo-G adduct (recently the mechanism of its formation was elucidated [38]). Analysis of nucleotide sequences in eukaryotes could show that there are ~14 proteins homologous to Umu C and DinB. They comprise several families and are classified in [31].

Though being "careless" the translesion polymerases are an indispensable element of cell equipment. Thus, pol gene knockout in mice makes embryo non-viable [39]. Because chromosome instability was observed augmented probably the gene is involved into DSB repair and may function as an oncosuppressor.

Regulation of translesion polymerases activity is an important biological problem. The results obtained showed that two proteins p53 and p21 determined which enzyme would be activated at the proper time

[40]. These proteins when functioning in the replicative fork can join an ubiquitin molecule to the clamp that works as an anchor enabling shifting of replicative enzyme to translesion polymerase. This yields minimum of mutations. If clamp proteins are damaged, the process of shifting loses its control.

The important factor of mutation induction under different conditions of cell functioning is the emergence of reactive oxygen species -ROS [41]. They are responsible for the appearance of 8-oxo-G adduct in genome. This can form a pair with any dNTP but dA or dC is preferable. dA/dC ratio is important for a kind of polymerases involved into the process.

Recently it was shown why ROS action leads to 8-oxo-G adduct formation [38]. Taking away an electron out of DNA by ROS results in the formation of an ionization hole in this molecule. The hole can migrate along its length and where two G are adjacent this migration is slowed down. This allows H_2O molecule to react with C8 of G converting it into 8-oxo-G adduct using the second water molecule and Na^+ as a counterion attracted by the negative charge of PO_4^- [38]. The elucidations of this adduct formation mechanism point out the importance of therapy with the aid of antioxidant compounds as the potential to slow down the spontaneous mutagenesis.

On the rates of spontaneous mutagenesis. It turned out that this rate could vary from organism to organism in the range of magnitude of several orders [6]. This pointed out that the cell is provided with a machinery to produce mutations as well as with a machinery to prevent them. Such a view was grounded by discovery of bacterial strains possessing either mutator or antimutator phenotypes. Details are described in [1], here we shortly discuss the following.

Identification of bacteriophage T4 gene encoding DNA polymerase enabled the study on the role of this gene mutations considering the rate of spontaneous mutagenesis. It was shown that some mutations led to mutator phenotype while others (very much infrequent or difficult to find) were real antimutators. It turned out that the replication fidelity depended on two points: precise selection of a right nucleotide during polymerization reaction and the value of relation of a polymerase activity to 3'-5' exonuclease (editing) activity. Some mutations lower this fidelity while others can increase it. This occurs when the time of a wrong nucleotide processing by exosite is increased due to alterations in the enzyme contact with the template [42]. Not only DNA polymerase gene but also some other genes may be involved in the determination of mutator or antimutator phenotypes. A gene called *tas* is an example [43]. ~10 genes of prokaryotic genomes were estimated as capable of influencing the processes of spontaneous mutagenesis [6].

The level of spontaneous mutations revealed in malignant cells could be accounted for an emerging of a mutator phenotype [44]. Interesting is the idea that not some special gene might be destined to function as a mutator but a transient mutator may appear as a result of errors during transcription or translation. Such an emerging transient mutator is capable of introducing mutations into genome [45].

Description of mutations dubbed adaptive and that appeared in the stressed cell unable to replicate its DNA and to divide [46] showed that the rate of spontaneous mutations might be significantly accelerated in the cell fighting for the survival. These mutations are characterized in [1] in details. Here we shortly mention that in the force majeure situation the cell may realize the potential to create a plethora of genotypes as if with a purpose to choose the fitter for the available conditions. A central role in increasing the rate of spontaneous mutagenesis belongs to the activation of genome sites responsible for possibility of DNA synthesis and recombination [47].

On the role of dNTP pool level *in vivo*, tautomeric transitions in DNA bases and mutations emergence. The level of dNTP pool *in vivo* can vary in the wide range depending on the status of genes responsible for these compounds metabolism and also on the environmental conditions (for example antifolate inhibitory action [48, 49]). To study if replication fidelity depends on dNTP concentration, the system for DNA synthesis *in vitro* can be used in which opposite T not only A but also its analogue as 2-aminopurine is inserted. It turned out that when dNTP concentration is high then the mutator polymerases make more mistakes. At low concentration this effect is not observed [14]. Therefore, the level of dNTP inside the cell is important for cell functioning. Since the polymerase editing activity seems repressed at high dNTP concentra-

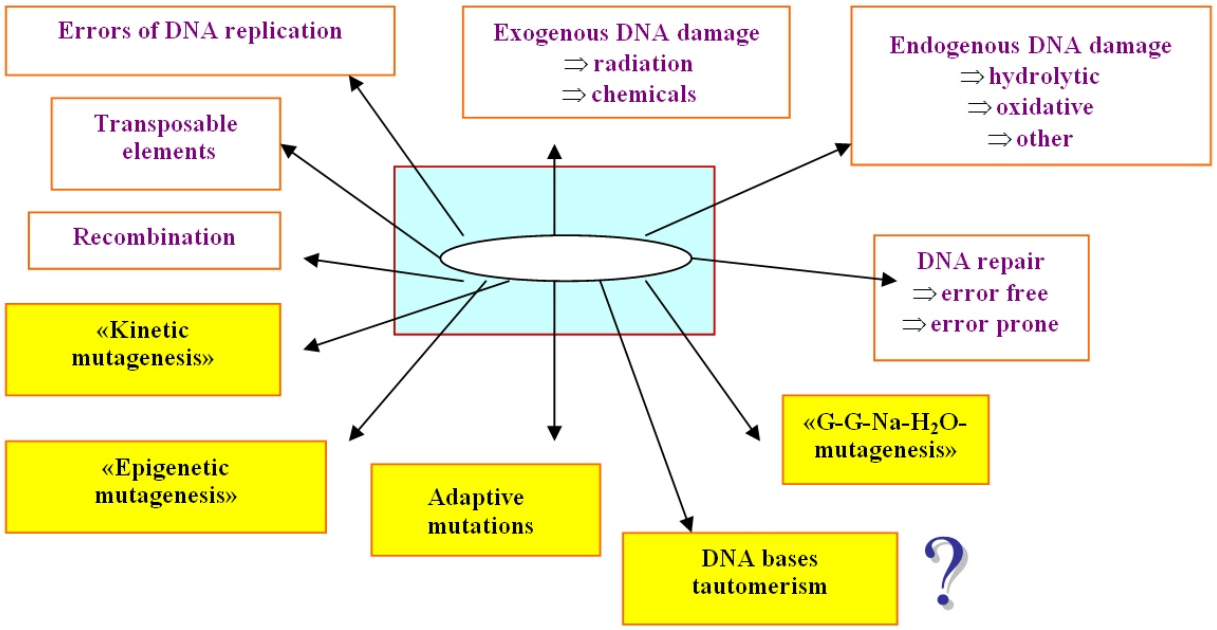

Fig. 2 Possible sources of spontaneous mutations ([15] added)

tion the special rule on the effect of the next nucleotide proofreading was formulated [50-52].

In the study of relationship between the dNTP concentration and the number of mutations induced it was shown that inactivation of deoxycytidylate deaminase gene increased dCTP/dTTP ratio in the cell greatly and the number of mutations grew [16].

Interesting effect was observed in temperature-sensitive bacterial strains called *mud* mutants. They are capable of growing at 42°C when and if adenine is added. Disbalance in dNTP pool was found in these strains; dATP, dGTP and dTTP contents were lowered while dCTP concentration was elevated [15]. The role of adenine in this effect still remains unknown [53]. In mammal cells also the link between the level of dNTP pool and the yield of mutations induced was shown [54, 55].

This link was also demonstrated in [56]. Here it was shown that in the genotoxically stressed yeast cells dNTP pool level was elevated about 4-fold over that for the S-period of the normal cell. This occurs due to deregulation of ribonucleotide-reductase - RNR activity. As for mutations observed in the cells with deregulated RNR the number of mutations appeared increased 2-fold in case if cell DNA was and 3-fold if DNA was not damaged. The first result could be accounted for a functioning of translesion polymerases but how could the second result be explained?

We suggest that this could occur due to the elevation at the tight molecular space overcrowded with dNTP of concentration of tautomeric forms of DNA bases resulting from proton tautomeric transitions from one to another atom of the base molecule. The tautomer forms emerged are prone to mispairing [13 and references therein] and thus could be the source of spontaneous mutations too. This possibility remains to be studied experimentally and the progress in nanotechnology and technology of fluorescent labels may have an encouraging effect to study this possibility.

Conclusions. The study on possible sources of spontaneous mutations showed that mutations are an immanent property of life. They serve as an efficacious tool in creating genetic diversity and directing biological evolution making life theoretically non-eradicated. Mutations can appear both as the result of some programmed as well as non-programmed events. Harnessing the rates of spontaneous mutations emergence is important not only in genetic diseases control but also in medication especially with targeted drugs of different diseases considering drug resistance problem related to mutation induction. In attempt to control this

rate different possible sources of spontaneous mutagenesis must be considered and among them such a phenomenon as tautomerism of DNA bases. The results summarized in this review show that an antioxidant therapy and the therapy controlling the level of dNTP pool as well as using drugs correcting the pattern of DNA methylation are important in the attempt to lower the rate of spontaneous mutations appearance.

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Современная картина спонтанного мутагенеза и возможное место в ней природной таутомерии оснований ДНК

Резюме

Суммированы данные по изучению всевозможных источников спонтанного мутагенеза, определяемого внутриклеточными процессами жизнедеятельности клетки в различных условиях ее функционирования. Охарактеризованы механизмы возникновения подавляющего числа классов мутаций, а также возможные механизмы регуляции скорости спонтанного мутагенеза. Анализ данных значительного повышения пула дНТФ в клетках в условиях генотоксического стресса и соответствующего повышения уровня мутаций в таких клетках позволяет объяснить наблюдаемый результат эффектами таутомерии оснований ДНК, происходящими при столпотворении этих молекул в тесном молекулярном пространстве. Предполагается, что контроль над скоростью спонтанного мутагенеза может быть связан с контролем над концентрацией дНТФ в клетке.

Ключевые слова: спонтанный мутагенез, таутомерия оснований ДНК, уровни внутриклеточного пула дНТФ.

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