DNA repair

The process of restoring the original native DNA structure is called DNA repair, or genetic repair, and the systems involved in it are called repair systems. DNA repair is one of the most important genetic processes in a cell, ensuring its vital activity and the preservation of the species as a whole.

Violations of the primary DNA structure

The main supplier of errors in the nucleotide sequence is DNA replication. The length of its molecule in humans is more than 3 billion. of nucleotides.

Disorders in the primary DNA structure may be caused by:

pairing errors (the base in the DNA template chain may be in a different tautomeric form for a short time, allowing the wrong base to be attached in the complementary chain: the most common error of this type is the insertion of adenine instead of cytosine to form an AG pair,

spontaneous cleavage of the base from the DNA chain (for example, depurination - cleavage of purines),

deamination of cytosine (and, as a result, by converting it into uracil),

by attaching methyl or ethyl groups to bases (this leads to a change in the properties of the base and, as a result, to the formation of an incorrect pair).

DNA damage can be induced by external influences: ultraviolet, X-rays, chemical compounds, etc. For example, ultraviolet radiation (UVB) causes crosslinking of neighboring thymine bases in the DNA chain. The thymine dimers formed in this process interfere with normal replication. Mitomycin C, some mustard gas and psoralenes lead to crosslinking of two DNA strands. Exposure to X-rays can cause single-chain breaks. Harsher radiation can lead to the formation of double-stranded DNA breaks.

Classification of DNA repair

1. In relation to the replication process, there are

A) pre-replicative repair - occurs in the G1 period of the cell cycle (for example, photoreactivation repair, excision repair)

B) post-replicative repair (carried out using mechanisms involved in the processes of DNA recombination and replication).

2 By the nature of the ongoing processes !!! Attention!!! It is necessary to pay attention to the name of the enzymes and the nature of their action.

A) Photoreactivation (light repair)

In 1949, A. Kellner and in 1950, R. Dulbecco established that the viability of actinomycetes and bacteria exposed to UV in lethal doses is restored if they are then exposed to visible light. The phenomenon was called photoreactivation. The reducing effect of photoreactivation is associated with the action of an enzyme, deoxyriboside pyrimidine photolyase (hereinafter photolyase), which is a polypeptide associated with a small RNA molecule (10-15 nucleotides) for its activity. This enzyme cleaves dimers of two neighboring cyclobutane-type pyrimidines in the same DNA chain, which are formed under the influence of UV rays. The enzyme attaches to them both in the dark and in the light, but the reaction of cleavage of bonds connecting two pyrimidine molecules is energetically dependent on the action of visible light with a longer wavelength. In light,

pyrimidine dimers are cleaved by breaking covalent bonds, monomerization occurs, and thus the normal DNA structure is restored. The effective range (365-490 nm) includes the longest wavelength UV rays (365-390 nm) and adjacent visible blue rays (435-495 nm).

The highest efficiency of photoreactivation was noted for the blue part of the visible spectrum. This is almost the only known enzyme reaction in which the activation factor is not chemical energy, but the energy of visible light. Deoxyriboside pyrimidine photolyase is widespread in various organic forms and is present even in such primitive microorganisms as mycoplasmas. All the bacteria studied have it, except Micrococcus radiodurans, which are extremely resistant to UV rays and withstand doses 1,000 times higher than those lethal to E. coli. Photolyase is found in the cells of many plants and animals, including humans.

B) Excision DNA repair

There are genetic repair systems in which damaged areas are cut out of the DNA chain, hence the term "excision repair". The general scheme of excision repair includes several stages: 1. Recognition of damage by **endonuclease** 2. Incision of the DNA chain by **endonuclease** on both sides of the damage; 3. Excision and removal of the DNA fragment containing the damage occurs with the participation of a **helicase**, an enzyme that unwinds the DNA molecule to release the ends after the primary incisions; 4. Resynthesis, during which **DNA polymerase** fills the formed defect in DNA due to its 5-3 polymerase activity. In other words, DNA polymerase synthesizes the missing DNA section in accordance with the principle of complementarity. 5. **DNA ligase** covalently attaches a newly synthesized DNA region to previously synthesized DNA. In general, excision repair usually recognizes violations of the secondary structure of DNA (double helix) and eliminates them.

C) Correction of mating errors (mismatch repair) as a specific variant of excision repair.

Mismatch repair corrects errors resulting from a violation of the complementarity of A-T or G-C pairs in the daughter chain when non-complementary nucleotides are included in them. The peculiarity of this mechanism is that it is able to distinguish the "old" DNA chain from the "new" one and correct the newly synthesized one. This phenomenon is based on the important property that the mother chain carries adenines in GATC sequences with methyl groups attached to them immediately after the end of replication. As a result, during the next replication cycle, the parent and daughter chains become structurally different, since the daughter chain remains unmethylated until the end of this cycle. It is during this time period that the base pairing errors should be corrected. Genetic repair of unpaired bases has been found in both human and yeast cells. Stages of the process:

- the MutS protein is attached to a pair of non-complementary bases, then the MutL protein is attached to this complex.

- the formed three-component complex activates the mutH protein (which is in an inactive, latent state in the cell) and binds to the nearest unmethylated GATC sequence.

- active mutH cuts the daughter chain of DNA near adenine, another endonuclease is activated. As a result, a fragment of the new chain containing the mismatch is deleted.

- see points 4 and 5 of the excision repair.

D) SOS-Repair

There are genetic repair systems in which the synthesis accuracy is low. They are inducible, and are caused by the need for DNA synthesis even on a matrix containing damage. In this case, DNA synthesis on a matrix that remains intact will be accompanied by a large number of errors. Although such DNA contains a significant number of errors, damaged cells do "escape" at some stage, unless vital functions are hopelessly disrupted. Due to the life-saving functions of this DNA repair system, it has been called SOS-repair. Thus, an important feature of prokaryotic and eukaryotic cells is their ability to increase the efficiency of genetic repair at a high dose of damage. This is possible as a result of the induction of a new or modification of one of the pre-existing DNA polymerases due to protein products of genes activated by damaging agents. For example, the appearance of such enzymes in the case of UV irradiation ensures the transdimeric synthesis of DNA, as a result of which there will be no gap opposite the thymine dimer, but a nucleotide. Of course, such an arbitrary substitution of a nucleotide into a newly formed DNA chain often leads to replication errors. Apparently, the accumulation of single-stranded DNA breaks is a direct incentive to trigger SOS repair mechanisms.

Diseases related to DNA repair disorders

Xeroderma pigmentosa

Cockayne syndrome

Trichotiodystrophy

Ataxia-telangiectasia (Louis-Bar syndrome)

Fanconi anemia

Hutchinson-Guilford syndrome (progeria!)

Werner's syndrome (progeria!)

A source:

Генетика. Учебник для вузов / Под ред. Академика АМН В.И. Иванова. – М.: ИКЦ «Академкнига», 2006.- 638 с