Mutagens and mutagenesis

Mutagens are factors capable of causing mutations.

Physical

ionizing radiation
: electromagnetic radiation with a shorter wavelength and greater energy than visible radiation (X-rays, gamma rays, cosmic rays);

increased body temperature.

Ionizing radiation

- It has **high energy** and passes through tissues.
- When passing through tissues, collisions with atoms and the release of their electrons occur → free radicals and ions (H^+, OH^-) are formed along the path of the beam, which can react with other molecules cellular structures, including DNA.
- DNA molecules can also be affected by radiation.
- Ionizing radiation mainly causes oxidation of bases and breaks the pentose-phosphate bond in the DNA chain.
- The mutagenic effect of irradiation depends on the amount of ions formed.

- *Absorbed dose of radiation*
  - is given in units of gray [Gy = J/kg].

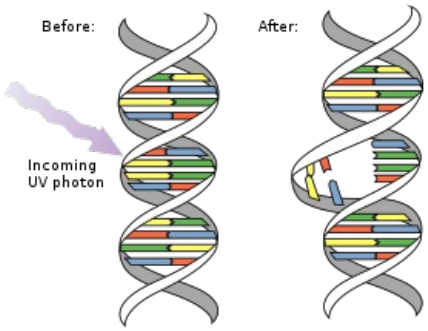
The mutagenic effect depends on:

1. doses;
2. exposure time;
3. cell cycle phase;
4. on the quality of repair mechanisms.

- It primarily causes chromosomal breaks and subsequently chromosomal rearrangements; event gene mutations.
- There is no threshold dose for radiation, and even individual quanta can induce mutation.
- The size of the radiation dose, which doubles the frequency of mutations in humans, is important in genetics for risk prediction - especially in the etiology of neoplasia.

Ultraviolet (UV) radiation

- It has considerably less energy than ionizing radiation, but UV radiation is also capable of increasing the energy of the electron of the affected atom (excitation).
- UV radiation is absorbed by many organic molecules, especially purines and pyrimidines.
- UV radiation is a strong mutagen for unicellular organisms; in multicellular, it damages only their surface cells.
- It can cause neoplasia of the skin (carcinomas, melanomas) in humans.
- The risk of UV radiation now increases as the ozone content in the upper atmosphere decreases.
- UV radiation causes mutations primarily through the formation of purine hydrates and pyrimidine dimers.
- Thymine mutations cause mutations in two ways:
  - disrupts the double helix structure of DNA and prevents DNA polymerase from following the template, thus interrupting DNA replication;
  - when reparing them, databases may be '*erroneously included*.
- Repeated interruption of thymine dimer replication without repair of the resulting gap in the newly synthesized strands **causes a chromosome break**; other manifestations are caused by base substitutions and deletions.



Damage of the molecule DNA by UV radiation

Chemomutagens

- chemical substances with a mutagenic effect.
- food *dyes* of acridine nature.
- **smoking products** (cyclic hydrocarbons).
- components of flue gas and exhaust gases.
- components of plastic materials (PCBs – polychlorinated biphenyls).

Mechanisms of action of chemomutagens

1. Substances that cause mutations only during replication;
   - **base analogs** and acridine dyes.
2. Substances that are mutagenic when acting even on non-replicating DNA.
3. Substances that cause **alkylation,** *deamination* ***and*** *hydroxylation* of bases.

Base analogs

- The substances are structurally related to nucleotide bases and incorporated into DNA during replication.
- Deviations in their structure then cause **incorrect base pairing** and, as a result, mutations.
- They are especially important in the experimental study of mutagenesis processes.
- The most widely used base analogues are 2-aminouracil and 5-bromouracil.
  - **5-bromouracil (5-BU**) is a thymine analog:
    - the bromine atom replaces the methyl at C5 of the pyrimidine and increases the probability of a tautomeric shift;
    - in the enol-form, 5-BU pairs with guanine;
    - when the enol 5-BU is incorporated into the new chain, the keto form of 5-BU is paired with adenine during subsequent replication, resulting in a G:C or A:T transition.

Acridine dyes

- proflavin;
- **acridine blue**;
- induce a reading frame shift;
- molecules of bases intersperse between a pair of bases during replication and change the conformation of the DNA double helix;
- during replication there is then a deletion or insertion of one or more bases with all the phenotype consequences.

Alkylating agents

- Numerous chemicals that can be **donor alkyl groups**.
- The first described mutagen was "mustard" or its nitrogen derivative.
- Nitrosoguanidine is among the most effective mutagens from this group.
- The action of alkylating agents causes a change in base pairing by linking a methyl or ethyl group with thymine.
- Alkylating substances can induce all known types of mutations, incl. chromosomal breaks and chromosomal rearrangements.

Deamination agents

- They cause oxidative deamination of the amino group of adenine, guanine and cytosine.
- Classic representatives are nitric acid and nitrites.
- The amino group of bases is replaced by a keto group due to their action.
- Deamination changes the ability of a base to form hydrogen bonds.
- Hypoxanthine pairs with cytosine, uracil pairs with adenine.
- Deamination of bases causes transitions in both directions (C-G to A-T and A-T to C-G).
- Nitrogen oxides are produced when fossil fuels are burned; the main sources of emissions are electric power plants and automobile transport.
- Nitrites are used to preserve sausages → they threaten the cells of the digestive tract with mutations.

Hydroxylating agents

- They can change cytosine to hydroxylaminocytosine, which pairs with adenine → thus causing a unidirectional C-G to A-T transition.

Biological

Viruses

- During the lysogenic cycle, viruses can be incorporated into the host's DNA.
- The insertion of a virus into the DNA sequence of a gene affects its function – the gene is usually non-functional after its incorporation → tumors, chromosomal breaks.

Transposons

- Elements capable of moving from one place in the genome to another.
- There are two groups of transposable elements in the human genome:
  - **LINE** (*long interspred nuclear element*);
  - **SINE** (*short interspersed nuclear element*);
  - their movements in the genome can have a mutagenic effect.

Mutagen Testing

- Most mutations have a negative effect on human health, and mutagenic substances are usually also teratogenic and carcinogenic, therefore testing the mutagenic effect of substances is a standard part of mandatory certificates before they are put into practice.

Ames test

The *Ames test* evaluates the mutagenicity of substances and their metabolites. It uses defective strains of the bacterium "Salmonella typhimurium" that have a damaged gene for the production of histidine. In the presence of mutagens, reverse mutations occur and thus the resumption of histidine synthesis. The ability of bacteria affected by the test substance to grow on a medium without histidine is evaluated.

- The current wide range of methods tests both mutagenic effects and genotoxicity.

- Comprehensive protection of genotoxicity is ensured on 3 levels:
  1. environment monitoring;
  2. monitoring of biological effects;
     - information on the response of the human organism to the action of genotoxic substances, on exposure and the effectiveness of preventive measures;
  3. genetic monitoring;
     - epidemiological studies of the occurrence of spontaneous abortions, congenital developmental defects in relation to genotoxic substances.

Links

Related Articles

- Mutation
- Chromosomal Abnormalities
- Toxicogenetics

Source

- ŠTEFÁNEK, Jiří. *Medicína, nemoci, studium na 1. LF UK* [online]. [cit. 2010-02-11]. <http://www.stefajir.cz>.