Disorders of DNA repair mechanisms in tumor cells

During human life genome numerous mutagenic effects (UV radiation, ionizing radiation), oxygen radicals, chemicals) therefore exist in the human body repair mechanisms, which they can repair DNA at different levels. If the human body loses these mechanisms, the cells become senescent, apoptosis, or to produce a malignant clone. Repair mechanisms exist at six basic levels and are secured **DNA repair proteins**. Some are active in the S phase, where DNA duplication occurs.

The DNA repair system includes

1. *DNA sensory proteins*
2. *enzymes that remove damaged nucleotide bases*
3. *enzymes that restore the normal sequence of DNA*

Each of these steps is under the control of additional regulatory enzymes that control the on and off of DNA repairs as needed. Regulatory enzymes include: helicases,topoisomerase (DNA unfolding).

Sensory proteins include ATM (Ataxia telangiectasia mutated) and ATR (Ataxia telangiectasia related), which control the change of the DNA double helix. If they encounter a change, they themselves autophosphorylate and subsequently phosphorylate other protein kinases. For example: ATM-CHk2-Cdc25A. Cdc25 is a cell cycle activator. If it is phosphorylated, this protein is inactivated, degraded and the cell stops in the S phase cell cycle. Reparation may occur or the cell goes into apoptosis. However, once a mutation occurs in the ATM gene, the cell will not stop in the S phase of the cycle and will subsequently accumulate further mutations. Different types of repairs are different in different tissues. U **rapidly dividing cells** (hematopoietic cells) the system prevails **homologous recombination of DNA**, while in **post-replicating cells** the system prevails **joining non-homologous DNA ends**.

Tumors are caused, among other things, by the cell's inability to respond to its damage. If genes involved in cell repair are mutated in the germ line, the individual is at increased risk of developing various tumors. Among the most famous mutation belongs**BRCA1, BRCA2** (breast cancer, ovarian cancer, prostate in men). Patients who inherit one mutated allele have an increased risk of developing a tumor. However, the development of the disease occurs only after the inactivation of the second allele, for example, a somatic mutation caused by radiation. Inability to repair DNA can also occur due to somatic mutations, or silencing the function of genes that encode DNA repair cascade proteins. This silencing occurs, for example, by gene methylation. This can lead to secondary mutations that cause the tumor to progress to a higher degree of malignancy by activating other oncogenes or by overriding the function suppressor genes. Treatment then occurs chemotherapy.

Basic classification of disorders of DNA repair mechanisms in tumor cells

1. ***Reparative disorders that occur during the restoration of reparative nucleotide pairing (DNA mismatch repair)***
2. ***Nucleotide excision repair disorders***
3. ***Congenital disorders of double-stranded DNA breaks***
4. ***A group of proteins that are used in the repair of double-strand breaks by homologous recombination***

Reparative disorders that occur during the restoration of reparative nucleotide pairing (DNA mismatch repair)

Among the congenital defects in the genes involved in pairing nucleotides, belongs **hereditary non-polyposis carcinoma of the colon (HNPCC)**, **Lynch syndrome** . These diseases are characterized by cancer large intestine, especially caecum and ascending colon. In the case of poor nucleotide pairing (G-T replacement instead of normal A-T), the repair system finds and eliminates the error in the S-phase DNA synthesis. In HNPCC, an individual inherits one defective allele of one gene, and the second allele in colonic epithelial cells is lost during life.

A typical feature of nucleotide mismatches is the instability of microsatellites. Microsatellites are tandem repeats of one to six nucleotides. Individuals with HNPCC fluctuate in length, in contrast to healthy individuals, who remain the same throughout their lives. One of the most common genes affected in the germ line is **MSH2** (35 % cases) and **MLH1** (25 % cases). Under normal circumstances, these genes encode proteins that bind to DNA. This marks the location and then the error is corrected. There are suspicions of hereditary non-polyposis colon cancer ***Amsterdam criteria***. These include: at least three developmental relatives colorectal cancer, two consecutive generations are affected, one of the patients developed cancer under the age of 50. At the same time, adenomatous intestinal polyposis is ruled out.[1]

Nucleotide excision repair disorders

This group of repairs is most often involved in exogenous DNA damage (UV radiation, polycyclic aromatic hydrocarbons, aflatoxins, cisplatin chemotherapeutics). UV radiation causes the formation of pyrimidine dimers (thymine - thymine, thymine - cytosine). Repair mechanisms include two subsystems. **GGR (global genome repair)**, which takes care of DNA repairs of the whole genome and **TCR (transcription coupled repair)**, ensuring

the correction of defects during transcription. If a mutation occurs in both of these systems, a congenital autosomal recessive disease will develop ***Xeroderma pigmentosum***. All people with this disease are at increased risk of developing malignant skin tumors after exposure to UV radiation. Some also suffer from neurological problems (microcephaly, progressive dementia, low intellect). The skin is dry (xeroderma) with abnormal pigmentation. There are both hyperpigmented and hypopigmented deposits. For **skin tumors (basal cell carcinoma, squamous cell carcinoma of the skin) occurs at the age of 8**. Sporadic skin tumors usually develop after 5 decades.

Disorders of repair of double-stranded DNA breaks

The main disease we classify here is **ataxia telangiectasia**. This is a monogenic gene mutation **ATM**. The protein of this gene is used in the search for double-stranded DNA breaks. The mutated protein is shorter and causes **arrest disorder at cell cycle checkpoints (G1/S, G2/M)**. The clinical manifestations of this disease are cerebellar ataxia (a disorder of migration and degeneration of Purkinje cells in the cerebellum), early onset of the disease (about 3 years, but also earlier), telangiectasia on the ear, conjunctiva and elsewhere on the body. Patients are immunodeficient and highly radiosensitive (radiation therapy is not possible).Ataxia telangiectasia leads to **most often the development of T-cell leukemias and B-cell lymphomas**. Nijmegen breakage syndrome (NBS) and Berlin breakage syndrome (BBS) have the same clinical manifestations as this disease.(BBS).

A group of proteins that are used in the repair of double-strand breaks by homologous recombination

The best known genes that are involved in homologous recombination repair are **BRCA1** and **BRCA2**. Their disorder occurs in familial breast and ovarian cancers. The complementary strand of the second chromosome serves as a template for the disrupted strand of the DNA of the first chromosome. BRCA1 and BRCA2 gene proteins also affect cell cycle functions. Germline mutations in the BRCA1 gene cause **increased risk of ovarian and tube cancer**. Men then have **increased risk of prostate cancer**. In contrast to sporadic carcinomas, they occur at a younger age. A mutation in the BRCA2 gene predisposes to the development of breast cancer in women. Breast carcinomas that have mutated BRCA1 and BRCA2 genes show high proliferative activity and a high degree of malignancy. However, they differ in the expression of pro receptors estrogen andprogesteron. Ductal and medullary carcinomas occur in women with the BRCA1 mutation. Other diseases that are caused by a disorder in homologous recombination of DNA include **Fanconi's anemia**. The clinical manifestations are failing bone marrow (thrombocytopenia, anemia, neutropenia), which subsequently progresses to myelodysplastic syndrome or acute myeloid leukemia.

Links

Related articles

- (Proto)oncogenes
- Tumor suppressor genes
- Cell cycle

References

-

Reference

1.