Mutator genes, cell genome stability

Mutator genes

DNA repair genes control the stability of the cell genome. They are responsible for repairing DNA damage .

- Mutation or inactivation of these geneslead to the accumulation and maintenance of mutations in the cell and the instability of the genome.
- Increased frequency and accumulation of mutations in the cell is one of the causes of malignant transformation.
- The products of these genes are involved in the repair mechanisms of damaged DNA.
- Mutator genes, unlike oncogenes and tumor suppressor genes, do not give a cell the ability to proliferate uncontrollably by itself. Thus, mutation of mutator genes leads to an increased frequency (100-1000-fold) of mutated oncogenes and tumor suppressor genes.

Genes enabling the excisional correction process

These include genes whose products cause excision. Their recessive mutations cause a condition called xeroderma pigmentosum and Cockayn's syndrome, which are precancerous lesions with an increased susceptibility to skin cancers induced by UV exposure

"Mismatch" repair genes - mutations in Mismatch Repair genes

Another group of mutator genes. The encoded proteins correct the base misalignment during DNA replication (but not complementary)

- The manifestation of mutations of these genes is instability at the nucleotide level, instability of microsatellite loci (MIN) - microsatellite instability (incorrect base pairing causes changes in the length of microsatellite sequences - their lengthening or shortening).
- Instability of microsatellite sequence lengths leads to replication errors.
- Mutations are recessive.
- Microsatellite sequences are distributed throughout the genome and are inherited in length. They are repetitive sequences of dinucleotides or trinucleotides, there are 50,000-100,000 (CA) n repeats in the human genome.

Germline mutations, especially hMSH2 (human MutS homolog 2), hMLH1, hPMSI and hPMS2 genes are the basis of **hereditary non-polyposis colorectal cancer (HNPCC)** – inheritedautosomal dominantly, familial occurrence is considered to affect 3 or more family members with a The kinship coefficient 0,5 and an incidence disease before the age of 50.

- Familial occurrence of HNPCC accompanied only by the finding of cancer of the colon or rectum (so-called Lynch syndrome I).
- In addition, about 30% of HNPCC patients develop carcinomas in other organs (endometrium, pancreas, stomach, urinary tract). This is the so-called **Lynch syndrome II**.
- The HMSH2 (chrom. 2p15-p22), hMLH1 (chrom. 3p21.3), hPMSI (2q31-33) and hPMS2 (chrom. 7p22) genes are responsible for correcting base mismatches (MMRs). Their mutations predispose to Lynch syndrome.

The instability of microsatellites has been described as a characteristic phenotypic manifestation in other tumors – breast and lung cancers, GIT tumors, endometrium, and meningiomas. Defects of the DNA-repair mechanism contribute to the accumulation of genetic defects, support the progression of malignantly transformed cells.

Examples of investigated mutator genes

hMSH2	HNPCC, type 1, ovarian tumors, glioblastomas, T-cell lymphomas
hMSH6	HNPCC, type 5, ovarian tumors, endometrial cancer
hMLH	HNPCC, type 2, Turcott syndrome accompanied by glioblastomas and leukemias
hPMS1	the protein encoded by this gene forms heterodimers with the protein encoded by the hMLH1 gene, has been detected in mutated form in some HNPCCs
hPMS2	HNPCC, type 4, Turcott syndrome accompanied by glioblastomas

Turcott syndrome is clinically characterized as a coincidence of hereditary primary colon tumors (FAP or HNPCC) with tumors of the central nervous system or leukemia.

Defects of the DNA-repair mechanism contribute to the accumulation of genetic defects, support the **progression of** malignantly transformed cells.

Links

Related articles

- Mutation
- Tumor suppressor genes
- Oncogenes
- Chromosomal aberrations in the etiology of neoplasms

References

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