Causes of chromosomal aberrations

Numerical Chromosomal Abnormalities

The cause of **aneuploidy** (trisomy, monosomy) is **nondisjunction** - an error in the distribution of homologous chromosomes in I. meiotic division, or chromatids or II. meiotic division and fertilization of an abnormal disomic or nullisomic gamete. Another mechanism that leads to monosomy after fertilization of an abnormal gamete is the delay of the chromosome in anaphase and its non-incorporation into the daughter nucleus. Both of these errors can also occur postzygotic, then a **mosaic** is formed. If a chromosome segregation error affects all chromosomes, an abnormal unreduced gamete is produced.

Causes of Nondisjunction

The main cause of non-disjunction is considered to be *higher age of the mother* (the age of the mother affects the length of the first meiotic division, which in women already begins during embryonic development). Father's age does not have such a significant effect. Older maternal age exponentially increases the risk of nondisjunction in gametogenesis and the risk of trisomies in fetusu.

However, the incidence of monosomy 45,X and polyploidy *does not depend* on the age of the mother (monosomy X is more often caused by a delay in the chromosome in anaphase and its loss, most triploidy is caused by a fertilization error (so-called dispermia), tetraploidy it arises from endoreduplication - an error during the first division of the zygote).

Explanation of the dependence of the risk of trisomy on the age of the mother

'*Aging of the egg*, insufficient hormonal activity and other factors associated with aging can contribute to the error in the distribution of chromosomes - *nondisjunction*, especially in the first meiotic division. It was found that the frequency of chromosome recombination decreases with age. Since chiasmata stabilize bivalents in the late prophase of meiotic division I, if recombination does not occur, the bivalent breaks up into univalents prematurely, or prematurely separate chromatids (they can start to separate already in the first meiotic division). This is believed to be the immediate cause of chromosome mis-segregation and the formation of abnormal gametes.

We know much less about the causes of chromosome delay in anaphase and its loss, which leads to a nullisomic gamete, or a monosomic cell line (if it occurs postzygotically). But it is known that the somatic loss of one gonosomes affects the cells of older women (it also occurs in men), as we can detect in peripheral lymphocytes. Apparently, this is an insufficient function of the mechanism that controls the connection of chromosomes to the dividing spindle (function of the kinetochore, kinetochore proteins).

Abnormal segregation of chromosomes in anaphase can also be the result of a mutation of one of the genes, which with their products participate in the control of mitotic division (control of the connection of kinetochores to the dividing spindle). Such mutations lead to chromosomal instability, i.e. numerical changes of chromosomes, which are described in tumor cells.

Parental origin of aneuploid gametes

The study of polymorphic molecular markers showed that nondisjunction most often occurs in oogenesis, more often in the I. meiotic division than in the II. meiotic division.

Trisomy 21

90% of errors arise in oogenesis, only 10% in spermiogenesis. 73% of maternal nondisjunctions of chromosome 21 arise in the I. meiotic division, 25% in the II. meiotic division, 2% of nondisjunctions arise postzygotically. The predominance of errors in the first meiotic division in maternal meiosis also applies to other trisomies (trisomies 18, 13, XXX and others). It is interesting that the lethal trisomy 16, common in miscarriages but not occurring in live births, is only of maternal origin (error always in the first meiotic division).

🔎 *For more information see Down Syndrome.*

Karyotype 47,XXY

It is caused by an error (nondisjunction) on the mother's side only in 54%, the error is again more frequent in the first meiotic division.

🔎 *For more information see Klinefelter Syndrome.*

Monosomy X

78% of all X monosomies result from the loss of a paternal gonosome, this loss is apparently postzygotic, at least in live-born X monosomies. Only 1% of all resulting X monosomies are reported to survive, presumably the X monosomy is lethal, and all surviving X monosomies are actually mosaics although often unrecognized mosaics. If Y chromosome is lost, it is lost very early.

🔎 *For more information see Turner Syndrome.*

Structural aberration of chromosomes

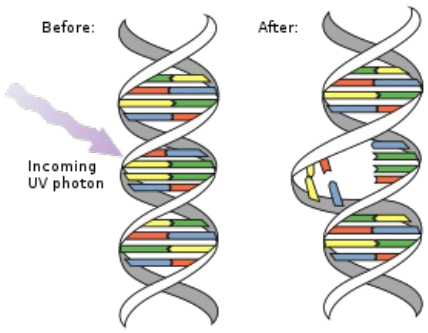
Causes of structural aberrations

Structural chromosome aberrations are the result of breaks, ev. their incorrect connection. They arise due to the action of exogenous, but also endogenous factors. We refer to factors that have the ability to produce chromosome breaks as **clastogens*. The critical lesion for the formation of structural aberrations are double-stranded breaks DNA* (abbreviation used in the literature is** DSBs **= d'ouble *s*trand *b*reak') and chromosomal aberration is actually the result of unrepaired or incorrectly repaired DNA damage.**

Formation of DNA double-strand breaks (DSB)

'*Endogenously* DNA breaks arise during oxidative metabolism, by the action of topoisomerase. During DNA replication and repair, DNA recombination (crossing-over in meiosis), during somatic recombination of immunoglobulin genes , i.e. during natural cellular processes. Single-strand breaks can be converted to double-strand breaks during replication.

Exogenous factors with clastogenic effects include radiation (ionizing, UV), chemical substances (alkylating substances, base analogues, alkyl epoxides, aromatic amines, nitro compounds, heavy metals) or restriction endonucleases. DNA double-strand breaks can be induced *directly* (ionizing radiation), or *indirectly* (UV radiation, free radicals, chemicals or their metabolites), when primary DNA damage (alkylation, hydroxylation or other base alteration) is transformed into single-stranded and then double-stranded DNA breaks by enzymatic] repair.



Damage of the molecule DNA by UV radiation

DSB repair

DSBs are repaired in two ways:

1. **Homologous recombination'** requires the presence of homologous sequences, i.e. the presence of a sister chromatid (it therefore takes place in the S or G2 phases of the mitotic cell cycle), or the presence of a homologous chromosome (the way in which meiotic recombination takes place)
2. **Non-homologous joining of broken ends** takes place mainly in the G0, G1 phases of the cell cycle, i.e. without the presence of a homologous template, but it can take place in all phases of the cell cycle. Somatic recombination of immunoglobulin genes, genes for T cell receptors and isotype rearrangement also takes place in this way. This second method of joining breaks is more error-prone because it uses short homologies located near the broken ends of the chromosomes and repair of the broken ends, which can lead to submicroscopic deletions or insertions at the breakpoints when they are joined.

Both methods – homologous recombination and non-homologous joining of broken ends of chromosomes – can lead to error-free DSB elimination as well as mutations and chromosomal aberrations due to faulty repair.

A **predisposing factor** for the emergence of breaks and structural rearrangements of chromosomes can be **transposable elements (transposons)**, which, when integrated into the genome, represent regions that are not homologous, which can activate repair mechanisms and induce the formation of breaks and submicroscopic interstitial deletions. Another predisposing factor for the occurrence of breaks are **repeated (repetitive) sequences scattered throughout the genome'**, created by retrotransposition and fixed in the genome (*LINEs = l**ong** in* **terspersed** e**element**, ***SINE** = **s**hort **in'**terspersed **e** elements). These sequences form single-stranded loops that are recognized by the DNA repair mechanism, which can also lead to small deletions. Scattered throughout the genome, repeats represent areas of homology between different chromosomes, in the case of breaks in these places, this can lead to Robertsonian or reciprocal translocations, as well as inversely repetitive sequences can be the cause of submicroscopic inversions. The presence of these scattered repetitive sequences is the reason for the non-random distribution of breaks, the so-called "hot spots" in the occurrence of chromosomal aberrations.*

Chromatid and chromosome aberrations

The **type of aberration** depends on the type of clastogenic agent and the phase of the cell cycle in which the clastogen acts.

Example: **ionizing radiation'** - irradiation of human lymphocytes (in the G0 phase) leads to aberrations of the chromosome type after cultivation (dicenters and rings, breaks of both chromatids), but irradiation in the G2 phase (in vitro during cultivation) leads to chromatid aberrations (ionizing radiation is independent of S phase).

Substances called radiomimetics (e.g. bleomycin) have effects similar to radiation. Most chemicals cause chromatid aberrations because they act in the S phase of the cell cycle, i.e. aberrations arise during replication (chemical substances dependent on the S phase).

Chromosome aberrations are considered to be a manifestation of an early genotoxic effect, an increased level of chromosome aberrations detected in an individual's peripheral lymphocytes is a certain predictor (biomarker) of the risk of cancer (tumors – a consequence of a late genotoxic effect).

Links

Related Articles

- Chromosomal Abnormalities
  - Numerical chromosomal abnormalities
  - Structural chromosomal aberrations
- Mutation
- Toxicogenetics
- Acquired chromosomal aberrations

References

- MILLER, O. J. a E THERMAN. *Human chromosomes.* 4. edition. New York : Springer, 2001. 501 s. ISBN 038795046X.

Odkazy

Související články

- Chromozomální abnormality
  - Numerické chromozomální abnormality
  - Strukturní chromozomální aberace
- Mutace
- Toxikogenetika
- Získané chromozomální aberace

Použitá literatura

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Kategorie:Genetika