Gene imprinting and human pathology

Gene imprinting in general

🔎 *For more information see Gene imprinting.*

Gene imprinting is a mechanism of gene expression regulation. Imprinted genes differ from Mendelian-inherited genes, in which, with the exception of genes on sex chromosomes, both alleles are normally expressed (transcribed). Imprinted genes are transcribed **from only one allele**, namely the allele of **a certain parental origin**. The second allele of the gene is **inactive - imprinted**. Imprinted genes are normally involved in **embryonic development**, regulation of proliferation, and have a function in behavioral development. Deregulation of imprinting is the cause of numerous human pathologies such as **gestational trophoblastic disease**, **Prader-Willi**, **Angelman** and **Beckwith-Wiedemann syndromes** and also plays an important role **in the development of tumors**.

Pathology associated with imprinting disorder

Numerous human pathologies result from dysregulation of imprinting.

Hydatidiform moles

Complete hydatidiform mole is caused by **sperm dispersion** or **duplication** in an enucleated egg, **ovarian teratoma** is the result of parthenogenetic development of an unfertilized egg. In both cases, only a single parental genome is present, but **the consequences are different** if it is paternal or maternal.

Triploidy

🔎 *For more information see Numerical chromosomal abnormalities.*

Differences in the manifestation **of triploidy** depending on the parental origin of the supernumerary set of chromosomes also indicate different activity of paternal and maternal alleles. If the supernumerary set of chromosomes in triploidy is **paternal**, the consequence of this abnormality is **trophoblast hypertrophy** (hydatiform moles partial), if the supernumerary set of chromosomes is **maternal**, the extraembryonic tissues are **reduced**.

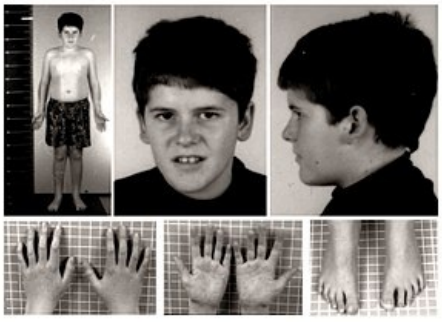
It is obvious that at the beginning of embryonic development, the active **paternal alleles** are preferentially involved in **the development of the membranes**, the active **maternal** alleles are preferentially applied during **the development of the embryo**, and a balanced action of both parental genomes is necessary for the successful development of an individual.

Prader-Willi syndrome and Angelman syndrome

🔎 *For more information see Prader-Willi syndrome, Angelman syndrome.*

Prader-Willi syndrome (PWS) and **Angelman syndrome** (AS) are two clinically different syndromes:

- **PWS**: obesity, short stature, small hands and feet, hypotonia, hypogonadism, mental retardation
- **AS** also "happy puppet syndrome": facial dysmorphia, severe developmental delay, jerky movements, bouts of inappropriate laughter



A 15-year-old boy with Prader-Willi syndrome

Both syndromes are associated with two **reciprocally imprinted regions** in the proximal region of the long arms **of the 15th chromosome** (15q11-13), with active genes in the PWS region on the paternal chromosome and with an active gene or genes on the maternal chromosome in the adjacent AS region. About 70 % of patients with both syndromes have the same or almost the same **microdeletion** (loss of part of the chromosome) in the 15q11-13 region, **in patients with PWS it is always on the paternal chromosome, in patients with AS it is always on the maternal chromosome.**

In some patients without this deletion, **uniparental disomy** (UPD = presence of both chromosomes in a pair from one parent) is detected , maternal in patients with PWS and paternal in patients with AS. In a small percentage of patients with AS, a classic gene mutation (gene for ubiquitin ligase) has been found. A classic gene mutation has not been found in any patient with PWS, probably because multiple genes play a role in the etiology of PWS.

In approximately 5 % of patients with both syndromes, a defect - a faulty imprint - was detected as a result of a mutation or deletion of a controlling element, the so-called imprinting center (IC). In all cases, the essence of the disease is the lack of function of active alleles, **paternal in the PWS region**, which **leads to the PWS syndrome**, while **the lack of function of the active maternal allele** or alleles in the adjacent AS region **leads to the AS syndrome**.

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome (BWS) also **EMG syndrome** (**e**xomphalos, **m**acroglossia, **g**igantism) is a syndrome associated with **excessive growth** and **an increased risk of tumors**. It is associated with dysregulation of imprinting of one of the two groups of imprinted genes. The best studied is the region including two reciprocally imprinted genes – the gene for the growth factor **IGF2**, expressed from the paternal allele, and the **H19** gene, expressed from the maternal allele. In patients with BWS, paternal duplications are found on the short arms of chromosome 11 (region**11p15**), paternal UPD , deletion or translocation of the maternal allele H19 (the consequence is the activation of the maternal allele IGF2), or mutation or deletion of the controlling element, the so-called imprinting center. All this leads to **excessive production of the IGF2 product** and therefore to **manifestations of excessive growth** and the risk of tumors. A proportion of BWS patients have dysregulation of the second imprinted region at 11p15, where several genes are located, including the maternally expressed gene for the cyclin dependent kinase (CDK) inhibitor.

Cancer illnesses

Impairment of imprinting is also associated with **the formation of tumors**. Many of the genes involved in the regulation of cell division and proliferation - proto-oncogenes - **are imprinted**, thereby regulating their proper function in the cell. **Dysregulation of imprinting** leads to the activation of proto-oncogenes and thus to their excessive activity, or to the inactivation of tumor suppressor genes. Since **the imprinting polymorphism** of some of these genes also exists in the population, this means a **predisposition to tumors**, e.g. in persons with monoallelic expression of tumor suppressor genes (WT1).

Mechanism of inactivation of an imprinted allele

A key role in the inactivation of an imprinted allele is played by **methylation**, the related **deacetylation of histones** and **the remodeling of chromatin** into an inactive form. Other regulatory mechanisms are also applied in imprinted regions, such as **the nuclear binding factor CTCF**, which binds to unmethylated sequences of the imprinting control element and thus **prevents the access of enhancers** to IGF2 on the maternal chromosome. The inactivation of paternal alleles can be ensured by so-called **antisense transcripts**, transcribed from the paternal allele, in the opposite direction to the sense allele. In imprinted regions there are also genes that do not have a protein product and function as mRNA, apparently also have regulatory functions (e.g. gene H19).

The regulation of imprinted regions of genes involves various mechanisms. The role of methylation in the inactivation of alleles is **crucial** and plays a role in the regulation of not only imprinted genes. It is known that methylation **disorder, especially genome demethylation, accompanies the process of carcinogenesis** and results in genomic instability. Demethylation of the genome also accompanies **the aging process**, and in this we can also see a causal **link between older age and tumors**. On the other hand, methylation, unlike mutations, is a reversible process and it is a realistic assumption that in the future it will be possible to use pharmacological manipulation of methylation to **treat tumors** associated with a defect in methylation or imprinting. Another hope is the possibility of using inhibitory proteins and interfering RNA to inhibit gene activity, this could be much more targeted than manipulating methylation. A better understanding of the mechanisms of gene expression regulation, including imprinting, is a prerequisite for the use of these promising procedures in the treatment of tumors.

Links

Related articles

- Gene imprinting
- Chromosomal abnormalities
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Source

- POLÍVKOVÁ, Z. Imprinting genů a lidské patologie. *Čas. Lék. čes..* 2005, y. 144, vol. 4, p. 245-250, ISSN 1803-6597.