Pancreatic carcinoma (genetics)

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According to molecular biological findings, pancreatic cancer is primarily a genetic disease. The exact sequence of somatic DNA mutations was traced. Similar to most cancers, it is a multi-stage process, the cumulative effect of acquired mutations in coding and regulatory genes, ploidy changes, gene amplification, structural rearrangements, deletions or loss of heterozygosity (in in the case of a congenital mutation of one tumorsuppressor).

The most frequent mutations occur in proto-oncogenes *K-ras*, *HER2/neu* and tumor suppressor genes *p16*, *p53* , *BRCA2* and *DPC4/SMAD4*. Their meaning will be described below. For gene damage to manifest, the general rule is that for proto-oncogenes, only one of the two copies of the gene needs to be mutated, and for tumor suppressor genes, both copies of the gene must be damaged. On the basis of successive mutations and changes, models of the formation of pancreatic cancer were created describing the individual phases of cell transformation with changes in the appearance of ductal epithelium.

Molecular genetic mechanisms

Gene *K-ras*

The most frequently mutated oncogene in pancreatic cancer cells (up to 90% of all cases). It is located on the short arm of chromosome 12. Its product is a small GTP-binding protein associated with the cell membrane at its inner side, which mediates signal transmission in the protein kinase cascade system. This signaling pathway has a direct effect on the rate of the cell cycle. A typical mutation of the gene in exon 12 caused by the substitution of AMK glycine for valine or aspartate causes the loss of the GTPase function of the protein. Ultimately, the protein is constantly active and transmitting a signal. The cell is stimulated to grow and divide.

Gene *p16*

Tumor suppressor gene present on chromosome 9. Most often, deletion of both alleles occurs, or deletion of one allele and simultaneous mutation of the other. Inactivation occurs already in the early stages of cancer. The product of the "p16" gene is a protein capable of inhibiting the cyclin-CDK4 or cyclin-CDK6 complex in the G1 phase of the cell cycle, thereby regulating (stopping) the cycle. Its absence leads to uncontrolled cell growth.

Gene *p53*

Alteration of this tumor suppressor gene appears only in the later stages of cancer. The gene *p53* is located on chromosome 17 and its protein product affects the cell cycle - in the event of DNA damage, the cell cycle stops at the G1 checkpoint until the relevant section of DNA is repaired, or if the DNA cannot be repaired, it puts the cell into apoptosis . The product of mutated "p53" usually loses the ability to bind specific sections of DNA and thus influence the expression of, for example, the "p21" gene. Damage to the "p53" gene is also associated with its excessive expression.

Gene *DPC4*

DPC4 (deleted in pancreatic carcinoma) is located on chromosome 18. Its deletion is typical only for pancreatic cancer and occurs in later stages of cancer development. The protein product controls the signaling pathways of growth factors TGF-β, which regulates the cell cycle in the sense of attenuation, cycle arrest and apoptosis. In the absence of the DPC4 product, tumor growth occurs.

Gene *HER2*

The oncogene *HER2* (human epidermal growth factor receptor) is located on chromosome 17. Its amplification and subsequent increased expression of the product, which is the transmembrane glycoprotein receptor for EGF, often occurs. The receptor has its own tyrosine kinase activity. An increased amount of ligands for this receptor (EGF, TGF-α) was also observed in the field of pancreatic cancer.

Therapeutic options at the molecular level

Research in this area is mainly focused on intracellular signaling pathways of EGFR (receptor for epidermal growth factor, it is highly expressed) and mutated Ras protein.

EGFR

EGFR is a membrane receptor with its own tyrosine kinase activity, after ligand binding, two receptors dimerize and mutual autophosphorylation of the receptors' intracytoplasmic domains occurs. This autophosphorylation evokes an intracellular signaling pathway through the Ras protein and MAP kinases. Antibodies against EGFR – the part of

the molecule that extracellularly binds the ligand (competes with it for binding) – are currently used commercially, namely cetuximab and panitumumab (experimentally combined with gemcitabine). There are also two kinase inhibitors that bind to the intracytoplasmic catalytic domain of the receptor (gefitinib and erlotinib) and thus block autophosphorylation.

Ras protein

Ras protein is a small protein associated with the cell membrane. In its inactive form, it binds GDP, but when activated, it exchanges it for GTP. As long as it binds GTP, the Ras protein is active and transmits the signal. Normal Ras has its own GTPase activity – it hydrolyzes its GTP to GDP and is inactive again. Most mutations in the *K-ras* gene cause a loss of GTPase function or, even worse, the ability to activate itself. Such a Ras protein is constantly active. For therapy at the molecular level, the fact is used that even before the Ras protein is located at the cytoplasmic membrane, it undergoes a typical post-translational modification – the attachment of a farnesyl group, which is catalyzed by the enzyme farnesyl-protein transferase. Without the attachment of a farnesyl group, the Ras protein is non-functional. Farnesyl-protein transferase inhibitors have been successful in vitro and in vivo, but have failed in clinical trials. At the moment, attention is focused on the use of RNA interference, which again looks promising.

Literature

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