ETIOPATHOGENETIC MECHANISMS OF CARCINOGENESIS

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Abstract: *The appearance of the neoplastic process is based on a series of complex mechanisms which afect the structure of the DNA and the expression of several genes – genetic and epigenetic mechanisms. The importance of molecular mechanisms of cancerogenesis is multiple and it encounters its applicability in various fields of clinic oncology: diagnosis, prognostic, epidemiologic treatment.*

Cuvinte cheie: *mecanisme moleculare genetice şi epigenetice, oncogene, gene supresoare, protooncogene, virusuri oncogene*

Rezumat: *Apariţia procesului neoplazic are la bază o serie de mecanisme complexe care afectează structura ADN-ului şi expresia mai multor gene – mecanisme genetice şi epigenetice. Importanţa mecanismelor moleculare ale cancerogenezei sunt multiple şi îşi găsesc aplicabilitatea în diverse domenii ale oncologiei clinice: diagnostic, prognostic, tratament, epidemiologic.*

The studies in recent years have led to a new formulation of the concept of cancer that claims that at cellular level cancer is a genetic disease of the somatic cells.(18) The transition from a completely normal cell to a malignant cell is done through a series of mutations due to alteration of genes involved in regulating cell growth and intercellular interactions. They can occur during DNA synthesis and cell replication, as a result of exposure to carcinogens in the environment or can be inherited as mutations of germ cells.(18)

GENETIC MECHANISMS, EPIGENETIC, OF CARCINOGENESIS:

The correlation of mutagenic action, of chemical substances, physical, exposure to viral oncogenes infections are arguments in favour of the involvement of the genetic mechanisms, epigenetic, in cancer.(17) The genetic mutational mechanism is reflected in the quantitative abnormalities (changes in the number of chromosomes) or qualitative of the karyotype that characterize tumour cells.(10) The epigenetic mechanisms involved in the process of carcinogenesis can be: DNA hypomethylation and genomic imprinting phenomenon.(13) The main types of genetic mechanisms of carcinogenesis, represented by chromosomal changes, are: nucleotide polymorphism, amplification, modulation, chromosomal translocation, deletion.(11) This occurs at the level of proto-oncogenes, oncogenes, and anti-oncogenes.

Proto-oncogenes**:** are categories of normal cellular genes that, when suffering structural and functional changes under the action of carcinogens, contribute to the malignant cell transformation.(11) Of the 30,000 human genes about 50 are proto-oncogenes.(2)

Oncogenes**:** are genes whose expression is intimately associated with the transformation of normal cells into cancerous cells. Activation of oncogenes causes an increased predisposition to cancer.

Table no. 1. Representative oncogenic genes that activate human tumours (22)

Oncogenic gens	Cellular function	Activated types of tumours	Mechanism of activation
EGFR/HER	Growth factor receptor	Glioblastoma, breast and lung cancer	Mutation Amplification
HER2/Neu	Growth factor receptor	Gastric, breast, lung cancer	Amplification
PRAD1/Cyclin D1	Cell cycle regulator	Breast and esophageal cancer, lymphoma and parotid adenoma	Amplification Translation
K-ras, N-ras, H-ras	Protein G, Transduction signal	Breast carcinoma, pulmonary, colon, sarcoma	Mutation
B-Raf	Transduction signal	Multiple tumour types, melanoma	Mutation
src	Adhesion and cytoskeletal signal and other functions	Colon, breast, lung cancer sarcoma, melanoma	Unknown
Myc	Transcription factor	Multiple tumour types	Amplification Mutation
Myb	Transcription factor	Leukemia	Amplification Over-expression
Fas	Transcription factor	Multiple tumour types	Over-expression
Int2/FGF3	Growth factor	Gastric esophageal cancer, head and neck	Amplification

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There have been identified around 100 tumour suppressor genes and more than 100 dominant oncogenes involved in the carcinogenesis.(19) ***Anti-oncogenes or tumour suppressor genes***: are genes that encode the synthesis of proteins involved in maintaining normal cellular function (e.g.: proteins having a role in reorganization and repair of DNA, proteins that regulate the cell cycle, protein that mediate growth factor signal).(22) *Gene p53*: it is a prototype of a suppressor gene; is the molecular link between etiologic agents of cancer (carcinogenesis factors) and the developing process of oncogenesis.(10) In more than half of the cancers appear mutations of p53. In the future determining the type and number of mutations in both p53 and suppressor genes in other tissues of healthy individuals, could identify individuals at risk for cancer.(10,8)

Table no. 2. Representative tumour suppressor genes that inactivate human tumours or hereditary syndromes (22)

Tumour suppressor genes	**Cellular function**	**Inactivated types of tumours**	**Mechanism of inactivation**	**Hereditary syndromes with line of alleles inactivated (14)**
p53(9)	Cell cycle regulator	Multiple tumour types	Mutation	Li-Fraumeni
Rb	Cell cycle regulator	Retinoblastoma, pulmonary cancer, small cell, sarcoma	Deletion Mutation	Family retinoblastoma
APC	Cellular adhesion	Colon cancer	Deletion Mutation	Family adenomatosis
PTEN	Transduction signal, Adhesion	Glioblastoma, prostate and breast cancer	Deletion Mutation	Cowden's
hMSH2	DNA repair mechanisms	Colon, uterine cancer, melanoma	Mutation	Hereditary non-polyposis colon cancer
BRCA1		Breast and ovarian cancer	Mutation	Hereditary breast and ovarian cancer
BRCA2		Breast and ovarian cancer	Mutation	Hereditary breast and ovarian cancer
WT-1	Transcription factor	Wilms Tumour	Deletion Mutation	Wilms Tumour in children
NF-1	GTP-ase activator	Sarcoma, glioma	Deletion Mutation	Neurofibromatosis
NF-2	Cytoskeletal protein	Schwannom	Mutation	Neurofibromatosis
p16/CDKN2	Cell cycle regulator	Melanoma, esophageal, pancreatic cancer	Deletion Methylation Mutation	Family melanoma

Currently, it is assumed that out of 600 viruses known to be able to infect man, 150 have oncogenic potential. After penetration of the virus into a cell, it is processed and undergoes a series of changes: biological, morphological, the viral nucleic acid is multiplied by the formation of multiple copies of nucleic acid, each copy constituting the nucleic acid of a new virus – viral replication.(3) Oncogenes viruses in association with the mutations of pro-oncogenes, oncogenes and suppressor genes, have a role in carcinogenesis.(12)

Table no. 3. Types of human oncogenes viruses and types of cancer involved (22)

Oncogenes RNA viruses:

Group and viral family	*Cancers type*
Sarcomas virus	Rous Sarcoma
Chronic leukemia viruses HTLV1 HTLV2 HTLV3 and HIV	 Leukemia or lymphoma with T cells Hairy cell chronic leukemia AIDS

Table no. 4. Types of human oncogenes viruses and types of cancer involved (22)

Oncogenes DNA viruses:

Group and viral family	*Types of cancer*
Papova A – HPV	Anogenital carcinoma
Papova B - polyoma - SV-50 - JCV - BCV	Lymphomas, Kaposy Sarcoma Leukemia in children Kaposy Sarcoma, Young Sarcoma
Adenoviruses	Adenoma
Herpesviruses (Epstei-Barr virus)	Nasopharynx cancer, Burkitt lymphoma, Leukemia
Hepadnaviruses - HBV	Hepatocellular cancer

METABOLIC CONSEQUENCES AND PATHOGENETIC IMPLICATIONS OF NEOPLASTIC PROCESS

The main biochemical abnormalities of the oncogenesis process are: changes produced by initiators and tumour progression; decrease in specific activity of oxidases peroxidases;(12) the role of carbohydrate shown through glycan synthesis;(11) disturbance of antioxidant enzyme activities;(12) changes in growth factor activity;(11,21) disturbance of junctional communication; disturbance of cell adhesion and of substrate phenomena;(15) disturbance of topo-inhibiting and inhibition phenomena cell density-dependent.(14)

Some of the pathognomonic tumour growth factors involved in carcinogenesis are: epidermal growth factor (EGFR), tumor angiogenesis factor (TAF), platelet growth factor (PDGF). VEGF (vascular endothelial growth factor) together with EGFR and PDGF are pro-angiogenesis factors.(21) EGFR indicates the number of extracellular connections and, in cooperation with its counterpart HER2, points out the presence of proliferation and apoptosis.(13) Their amplification occurs in more than half of glioblastomas, breast cancer, and lung cancer.(22)

***Conclusion*:** The appearance of the neoplastic process is based on a series of complex mechanisms that affect DNA structure and the expression of several genes, genetic and epigenetic mechanisms. The progresses made in the field of molecular mechanisms of carcinogenesis are multiple, and find their applicability in various fields of clinical oncology:(13) diagnosis (classification of tumours, differential diagnosis between benign and malignant forms, early detection);prognosis (amplifications of oncogenes); treatment (suppression of oncogenes transcription – monoclonal antibodies and radiotherapy); epidemiology (genetic consultation).

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