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Genetic and epigenetic changes in malignant cells of tumors of urogenital organs

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More than 90 % of human malignant neoplasms are presented by epithelial tumors. Cancer of urogenital organs is a serious problem because of wide spread of disease and high mortality rates. Tumorogenesis is associated with different defects of genetic apparatus of cells as well as epigenetic factors (DNA methylation disorders, chromatin reorganizations in processes of histones modifications, regulation of gene expression with small non-coding RNAs). In this review we analyzed genetic and epigenetic changes in the urogenital tumors.

Keywords: cancer of urogenital organs, modifications of histones, DNA methylation, oncogenes, mutations.

Tumor (neoplasia) is defined as abnormal overgrowth of tissue with hereditary ability to unlimited and uncontrolled growth. More than 90% of human malignant neoplasms (MN) are presented by tumors of epithelial origin [1].

Most of such tumors appear in urogenital organs. It is difficult to cover all nosological MN forms of urogenital organs in a single review. Therefore we attempted to analyse genetic and epigenetic alterations in renal, prostate, cervical, and ovarian cancer.

The loss of adhesive functions and formation of invasive phenotype are recognized as crucial factors for malignization of epithelial cells. The tissue dedifferentiation and epithelial-mesenchymal transition are important events for the progression of epithelial tumors as well. Moreover, various types of cancer are characterized by dysfunction of tissue specific transcription factors, candidates for gene suppressors of tumors, i.e., hepatocytes nuclear factor (HNF), and in addition activation of oncogenes, immortalization, apoptosis suppression, and neoangiogenesis [2].

The structure of malignant tumor and its functional relationship with microenvironment are complicated. It shows itself as a distinct organ, able to use normal cells for angiogenesis, metastatic niche formation, and defence against immune response.

International TNM-classification of MN is currently accepted: T (tumor) – proliferation of primary tumor; N (nodes) – invasion in regional lymph nodes; M (metastases) – presence of metastases [3].

Cancer as a cause of death possesses the second place, it follows closely cardiovascular diseases. In 2006, the MN morbidity rate in Ukraine was 342 cases per 100,000 population with a tendency to increase, whereas mortality rate was 188 cases per 100,000 population [4].

The structure of morbidity/mortality in Ukraine is represented by such forms of urogenital cancer as (%): prostate – 7.4/6; renal (in men) – 3.5/3.1; cervical – 8.1/6.2; ovaries –6.3/4.9 [4].

Among ovarian carcinomas, the predominant forms by histological structure are serous (about 80%), endometrioid, mucosa, and clear cell tumors, which are the most aggressive types. The problem of ovarian cancer (OC) is considered to be one of the most important in current oncology due to peculiarities of etiology, pathogenesis and clinical course of the tumor development in this organ that leads to late diagnosis and poor survival of patients. OC ranks the third rate in the detection among all oncoginecological diseases in Ukraine (12.7 % of all MN among women aged 15-29 years) and the first in mortality rate. The highest mortality (8.3 %) is observed among women aged 30-54 years [4].

Squamous cell cancer is about 80 % of cervical malignant tumors, whereas adenocarcinomas and clear cell adenocarcinomas are not common. The papilloma virus infection contributes to the formation of both benign and malignant tumors. In the latter case, the disturbance of cervical epithelium structure occurs, preceding the development of invasive cancer. Cervical cancer (CC) has the second position in Ukraine, and the highest morbidity and mortality rates were registered among women aged 15-29 years (15.2 % of all MN) and 30-54 years (11.7 %) correspondently [4].

Renal carcinoma (RC) possesses the 10-th place among the most widespread forms of cancer that is approximately 3 % of all oncological diseases. Clear cell RC, granular cell RC, spindle cell RC, and columnar-cell renal cancers are distinguished. In Ukraine, the incidence of renal cancer in men aged 30-54 years reaches 5.3 % of all MN, and the number of patients with renal cell carcinoma (RCC) is annually increasing [4].

Adenocarcinomas are about 95 % of all prostatic cancers (PC), whereas transitional cell cancer and squamous cell cancer are less common. The substantial percentage of biopsies performed in patients with suspected oncopathology of this organ is defined as prostatic intraepithelial neoplasia (PIN). PIN is generally characterized by preservation of basal membrane integrity. The part of PC reaches 12 % of malignant tumors among men. During last years this disease is being diagnosed at younger age [4].

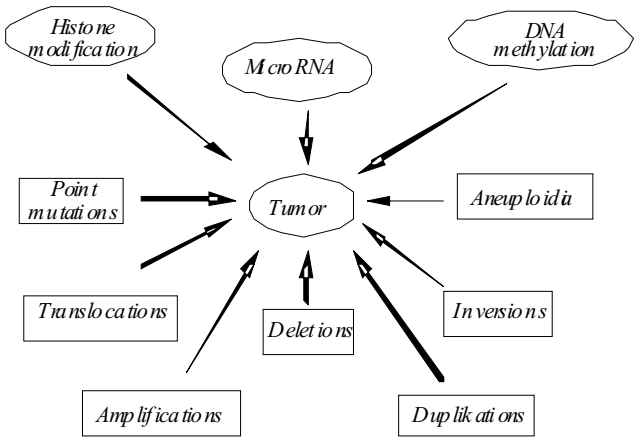
Therefore, urogenital cancer remains a serious problem in Ukraine due to its abundance and high mortality rate. The investigation of cancerogenesis peculiarities of given nosological MN forms on molecular level may help for their early diagnostics.

Mutations and chromosomal rearrangements in urogenital cancer. Basic study of cellular and molecular mechanisms of oncogenesis has revealed several genetic and epigenetic alterations that accompany the process of tumor development [5] (see Figure).

Various damages of cell genetic apparatus (somatic mutations, chromosomal aberrations) are known to be a base of malignant cell transformation. This may result in conversion of protooncogenes into oncogenes, shutdown of suppressive genes as well as dysfunction of the DNA post-replicative reparation system. Structural alterations of genes appear due to external or internal cancerogenic impacts. Additionally, high malignization risk is thought to be determined by inherent genotype damages.

The occurrence of certain chromosomal aberrations and mutations can correlate with several MN forms. Leukemias and lymphomas are mainly characterized by translocations, in particular, those of *myc*- gene [6]. However, the current data also indicate a role of translocations in the induction of solid tumors, including those of urogenital tract. Thus, the fused genes *PSF-TFE3* and *TMPRSS2-ERG* were found to appear in renal cancer [7] and PC [8] correspondently. The fused oncogenes encode chimeric proteins (transcription factors, proteinkinases). The sites of chromosome translocations in tumors proved to be associated with Z-DNA domains, and in 95 % of cases a correlation between genetic instability and Z-DNA is observed in mammals [9].

Amplifications are known to be caused by DNA replication disorder. They can be accompanied by DNA recombination and consequently its irregular distribution between daughter cells [10]. High amplification level of certain sites causes the formation of so-called pseudo-chromosomes (double-minute chromosome) [11]. Amplification of *myc* oncogene is



Epigenetic and genetic tumor induction factors

found in various cancer types [12], while amplification of *Notch3* and *PIK3CA* genes is frequent in OC [13]. Amplifications along with point mutations of *EGFR* gene are typical for serous ovarian cancer [14]. It is worth noticing that amplification of multiple drug resistance (*MDR*) genes advances the tumor resistance to anticancer drugs [15].

Aneuploidia appears as a result of dysfunction of cell division control and may be a cause of significant increase in chromosome number of tumor cells. In particular, cervical cancer is associated with aneuploidia of the both 3-rd and 17-th chromosomes [16]. At OC, the aneuploidic cell formation is related to the loss of GATA6 transcription factor expression with participation of microRNA [17].

Another few chromosomal rearrangements, such as inversion, deletions, insertions, and duplications, are rather frequent in carcinomas. For example, inversion of pericentromere region of the 9-th chromosome is associated with OC [18]. Also, a loss of function of imprinted gene *NOEY2* of the *RAS* family due to the deletion of active allele is a sign of ovarian cancer [19]. The involvement of *Alu*-repeats in duplication of the 13-th exon of *BRCA1* gene was revealed [20]. Moreover, *Alu*-repeats themselves were shown to contain insertion mutations in OC [21].

Various chromosome aberrations are likely to appear due to disorder of general regulative mechanism supporting normal chromosome segregation [10].

Point mutations of *RAS* oncogene acompany many MN [22]. Inactivation of a key gene, tumor growth suppressor *p53*, is induced by DNA recombination, aneuploidia, deletions as well as by point mutations. Mutations of *p53* gene were observed in many types of human tumors including urogenital cancer [[23]; mutations of *BRCA2* were found, in particular, in ovary cancer [[24]; mutations of *BRCA1* are linked with a block of stem cells differentiation and an increase of their population [25].

Genome instability is hereby considered to be the main cause of the tumor induction and development. It is manifested by progressive accumulation of mutations affecting basic vital functions of cells [26]. An important factor of cell transformation is currently believed to be the autocrine activation of cell proliferation resulting from the interaction of oncogene product with appropriate receptor located on the cell membrane or inside the cell [27].

However, it is necessary to keep in mind that an important role in tumor growth belongs to the microenvironment, whose components are in complex relationship with cancer cells.

Epigenetic alterations in urogenital cancer. Besides genetic aberrations, epigenetic factors (chromatin remodelling under histone modifications, regulation of gene expression with non-coding small RNAs, DNA methylation disorder) make a significant contribution to cancerogenesis that leads to alterations in the transcription of vast number of genes.

Histone modifications. Epigenetic mechanisms of realization of histone code act on the chromatin level thus programming the development of organism. Replication, recombination, reparation, and transcription are all controlled by the changes in structure and spatial organization of chromatin. It is well known that histones are conservative proteins. Nevertheless, there is a wide set of their covalent modifications determining the gene functional state. The role of Z-DNA in modulation of chromatin structure and posttranslational modifications of histone was also shown [28]. In turn, histone modifications can serve as a signal for DNA methylation [29].

A level of histone acetylation, which is reversible Lys modification in N-terminal domains of core histones, indicate a possibility of cancerogenesis. Thus, estrogen receptor (ER) initiates histone acetylation and activation of expression of genes taking

part in apoptosis regulation, immortalization, angiogenesis, and invasion. In contrast, BRCA1 provides histone deacetylation and ER ubiquitinization thereby blocking expression of downregulated genes [30]. In general, cancer cells are characterized by trimethylation of lysine 20 in histone H4 and loss of acetylation of lysine 16 [31]. Histone methyltransferases are involved in the tumor development (EZH2 – enhancer of zeste homolog 2) and suppression (RIZ1 – retinoblastoma protein-interacting zing finger protein) [32]. EZH2 was demonstrated to play a role in DNA methylation due to DNA-methyltransferases involvment and deacetylation of histones (in synergism with HDAC 1 and 2) [33].

Increase in HDAC activity (determined by histone deacetylases) is associated with tumor progression in solid MN including oncopathologies of urogenital organs [34]. Thus, expression of HDAC1 and HDAC2 significantly increases at dysplasia and cervical carcinoma. Moreover, E7 oncoprotein of herpes virus appears to be a component of enzyme complexes HDAC 1 and 2 [35].

HDAC1 high level correlates with unfavourable prognosis in endometrial carcinoma [36], while loss of trimethylation of lysine 27 in histone H3 is considered as a prognostic marker in ovarian cancer [37]. Histone acetyltransferase (HAT) Hbo1 promotes DNA replication, and overexpression of its gene is observed in the reviewed pathology [38].

It was shown that activation of HDAC3 and HDAC6 represses expression of Aurora A, a negative regulator of cell cycle, thus involved in renal cancer development [39]. In this case, overexpression of HDAC 1 and 2 is also observed [34]. Hypoxia inducible factor (HIF) provides histone demethylation through activation of histone demethylases (JMJD1 A and others) stimulating induction of renal carcinoma under hypoxia [40].

Demethylation of lysine 9 in histone H3 (H3K9me2) takes place in PC and RC and correlates with an increase in DNA repeats level. Dimethylation of lysine 4 and acetylation of lysine 18 in histone H4 also increase risk of prostatic cancer [41]. On the contrary, protein MCP30 promotes HDAC1 inhibition and histones H3 and H4 acetylation, thus suppressing the development of oncological disease [42]. Trimethylation profile of lysine 4 and lysine 27 in histone H3 [43] together with histone H3 phosphorilation [44] are considered as a prognostic factor at PC.

Revealing specific samples (signature) of acetyl and methyl histone labels is thought to be promising approach for diagnostics of urogenital tumors and prognosis of their development.

RNA-associated regulation of expression. The next important level of epigenetic regulation is provided by non-coding microRNA via binding with complementary site of appropriate mRNA resulting in its degradation and translation block. MicroRNAs are able to control the processes of histone modification and DNA methylation. Human genome contains over thousand of microRNA genes. Aberrant production of microRNAs is observed in tumors. MicroRNA sets are detected using recent microchip technologies [45].

It is known that malignization of epithelial cells is promoted by microRNA-205, whose expression is repressed by microRNA-184 [46]. MicroRNA-378 is capable of blocking caspase-3 activity and as a result promotes cancer cell survival and angiogenesis. Besides, it inhibits expression of the gene- suppressor of tumor growth FUS1 (fused in sarcoma) [47].

Changes in microRNA content and expression in MN of urogenital organs are being extensively studied. Thus, methylation of promotor of microRNA-34a gene inducing inactivation of the suppressor of tumor growth, which also promotes apoptosis and cell differentiation, is found in various malignant tumors including prostatic cancer [48].

The development of aggressive forms of solid tumors (in particular prostatic ones) is associated with the loss of expression of microRNA-449, the suppressor of histone methyltransferase EZH2 that consequently leads to survival and metastasis of cancer cells [32].

A decrease in microRNA-34a expression, that mainly targets HDAC1, is observed in prostatic cancer [49]. Over 50 microRNAs associated with the prostate malignization have been already recognized [45].

The blocking of microRNA-34a expression through the promotor hypermethylation is observed at KC as well [48]. Simultaneous presence of both

microRNA-141 and microRNA-156 is also observed in 97 % of samples of clear cell renal carcinoma [50].

Normally, ovarian microRNAs regulate oocyte maturation [51], however they can also be involved in MN formation [52]. In particular, the oncogene microRNA-21 expression is elevated due to DNA demethylation in ovarian cancer. The suppressor protein BRCA1 is targeted by microRNA-212 in serous carcinomas [53]. Hypermethylation of microRNA-129-2, the negative regulator of SOX-4 oncogene, correlating with microsatellite instability, is observed in endometrial cancer [54].

It was shown that the papilloma E6 viral protein leads to destabilization of p53, the transactivator of suppressor microRNA34a, resulting in consequent inactivation of the latter in cervical cancer [55].

Methylation of tumor suppressing microRNA-1 gene, which in turn targets histone deacetylase HDAC4, occurs with the aid of DNMT1 [56].

Since microRNAs fulfil both positive and negative regulation of tumor development, their expression profile is often associated with diagnosis, stages, progression, oncopathology prognosis, and therapeutic response. The perspectives of gene therapy are associated with the usage of microRNA for inactivation of oncogenic signal pathways or genes involved at cancerogenesis [57].

Alterations of DNA methylation status. Methylation provides X-chromosome inactivation, imprinting, regulation of tissue-specific gene expression, and control on genome stability. Methylation block is linked to embryogenesis arrest and apoptosis, while changes of methylation status - with oncogenesis [58].

CpG-islands and gene transcription. In mammals, most 5`-methylcytosines are concentrated in 5`-CpG-3`-dinucleotides. In CpG-islands frequency of CpG-dinucleotides is 5 times more comparing to other DNA fragments. These regions occupy 1-2 % of genome and have average size of 1,000 bp. [59]. CpG in these islands normally are not methylated except imprinted genes, whereas most CpG-dinucleotides outside the islands are methylated [60]. CpG-islands are distinguished by a high content of guanine and cytosine (G + C exceeds 60 %). Over 80 % of *NotI*-sites are linked with CpG -rich regions. The general feature of such islands is their localization in 5'-sites of genes, in regulative sequences or in the first exon [61].

Due to the structural homology between 5'-methylcytosine and thymine, methylation of cytosine residues can be accompanied with the formation of new transcription factor binding sites. This process affects transcription due to changes in binding efficacy of transcription factors with their regulatory sites on DNA molecule and the formation of transcriptionally inactive chromatin regions with participation of MeCP1 and MeCP2 proteins [62].

Methyl-DNA-binding proteins, containing methyl-binding domain (MBD), are capable of blocking TSG (tumor suppressor gene) transcription by interaction with their methylated promotors [63]. MBD1 protein, interacting with histone methyltransferase, is involved in the chromatin inactivation while MBD4 protein takes part in DNA reparation; its dysfunction promotes tumorogenesis [64]. An increased expression of *MBD2* gene correlates with its hypermethylation and progression of ovarian cancer, however, inverse relationship is observed in colorectal cancer [66].

Hypermethylation and urogenital cancer. Occurrence of MN in human is associated with imbalance of DNA methylation. Moreover, the correlation between aberrant methylation of CpG-islands and location of chromosomal breakage is observed in early periods of tumor development.

Methylation of promotor CpG-islands can inactivate both alleles of TSG, thus promoting malignization [67]. Besides, 5'-methylcytosine itself is able to induce mutation due to its instability. Structural proteins and transcription factors compete with methyltransferase for binding sites in CpG-islands. Therefore, such imbalance during cancerogenesis results in their aberrant methylation [68]. It was also shown that methylation of tumor-suppressing microRNAs was a prerequisite for metastasis [69].

It is important to note that an increase in the DNA-methyltransferase (DNMT) activity occurs as a result of p53 and Ras dysfunctions during cancerogenesis. *DNMT1* promotor is activated by the product of *H-ras* gene, which is involved in mitogenic signal transferring. In addition, the DNMT1 N-terminal domain is able to interact with histone

deacetylases in protein complexes of transcription repression, tumor suppressor Rb (retinoblastoma protein), replicative fork protein PCNA (proliferating cell nuclear antigen), thus participating in the malignant transformation process [70].

Aberrant methylation of several TSG is revealed in urogenital tumors. Thus, methylation of CpG-islands of the *OPCML* (opioid binding protein/cell adhesion molecule-like) promotor, with the decrease of its expression was observed in cervical cancer [71]. So, *OPCML* in fact is a candidate in TSG. It was also demonstrated the decrease in the expression level of corresponding protein as a result of *CADM* (cell adhesion molecule) gene methylation [72], while epigenetic shutdown of *DKK1* (dickkopf homolog 1) was revealed in the cell lines of cervical cancer [73].

Ovarian cancer is associated with aberrant methylation of *FANCF* (Fanconi anemia, complementation group F) gene. Its product is known to play a crucial role in DNA reparation [74]. Stratifin gene encodes transcription factor 14-3-3 and contributes to genome integrity through mitosis control. All of its 17 CpG-islands are methylated in OC [75].

In ovarian cancer, inactivation of TSG *ARHI* (anaplasia Ras homologue member 1), *PEG3* (paternally expressed gene 3), and *OPCML*, occurs as a result of heterozygosity loss and promotor methylation [76, 77]. Promotor methylation was also revealed for *DAPK* (dystrophin) [78], *DLEC1* (the deleted in lung and oesophageal cancer) [79], *RASSF1A* (RAS-association domain family member 1) in OC [80].

Hypermethylation also exists in PC [81], while inactivation of gene-suppressor *p16* by promotor hypermethylation occurs in renal carcinoma [82]. Epigenetic inactivation of oncosuppressor gene *BTG3* (B-Cell translocation gene 3) is observed in prostatic and renal cancers. Such inactivation by promotor hypermethylation and histone modifications (acetylation level changes of lysine in histone H3) is also documented for the negative regulator of the cell cycle [83, 84].

Methylation of *OPG* (osteoprotegerin) gene was revealed in cells of renal, ovarian and cervical carcinomas in parallel with the alteration of histone H3 methylation: elevation of lysine 27 and decrease of lysine 4 methylation [85].

Investigation of gene hypermethylation in tumors allows us to establish consistent patterns associated with disease progression or histological features. For example, aberrant promotor methylation of genes 14-3-3 , *TMS1* (target of methylation induced silencing), *WT1* (wilms tumor suppressor 1) is often observed in clear cell ovarian carcinoma [86-88], whereas hypermethylation of *RASSF1A*, *APC* (adenomatosis polyposis coli) and *GSTP1* (glutathione S-transferase 1) is only revealed in invasive ovarian carcinoma unlike the tumors with low malignization potential (LMP) [89]. Methylation of promotors of *APC* and *GSTP1* genes is considered to be prognostic marker for patients' survival [90].

Hypomethylation and cancer of urogenital system. In parallel with hypermethylation of CpG-islands in promotor regions of genes extensive hypomethylation takes place in genome of cancer cells [91] that is confirmed by evaluation of 5`-methylcytosine content in DNA [92]. A significant amount of hypomethylated genes including such oncogenes as *CMYC* and *HRAS* is observed in primary cancer [93].

Hypomethylation of *TUBB3* (tubulin beta, class 3) gene leads to its overexpression that provokes malignization and resistance to chemotherapy of ovarian cancer [94]. This pathology is also characterized by hypomethylation of *SERPINB5* (serpin peptidase inhibitor, class 5) [95], *SNCG* (synuclein, gamma) [96] and *CLDN4* (claudin 4) [97]. Elevation of hypomethylation simultaneously with increase of malignization degree is noted for several genes in ovarian and cervical cancers [65]. Therefore, DNA hypomethylation could be considered as a prognostic marker. Hypomethylation in tumor cells can cause transcriptional activity of mobile elements of genome, which in turn activate the oncogene transcription. Demethylation of promotors and expression of LINEs (long interspersed nuclear elements) are observed in various types of sporadic cancer [98]. Demethylation of satellite DNA is also found in cancer [93]. Thus, in normal somatic cells, pericentromeric heterochromatin regions on the 1-st chromosome are characterized by a high methylation status. Meanwhile, they appear to be demethylated in ovarian cancer. Moreover, more extensive hypomethylation of satellite DNA was shown in serous

and endometrioid ovarian carcinomas in comparison with mucinose one [99].

Total hypomethylation of constitutive heterochromatin can be accompanied by chromosomal translocations and aneuploidia at cancerogenesis.

Summarizing the data described herein, we can make the conclusion about interrelation not only between genetic and epigenetic mechanisms of gene expression control but also between various levels of epigenetic regulation.

Complexity and variability of epigenetic changes at MN are reflected in the current ideas on the existence of common signaling network ("functional network of human epigenetic silencing factors"). In particular, histone deacylase 1, DNA-methyltransferase 3a, histone lysine methyltransferase, and histone chaperone CHAF1A are involved in the network. This opens up new perspectives for the elucidation of molecular mechanisms of tumor genesis and for the selection of the most important targets at cancer therapy including oncopathologies of urogenital tracts.

В. В. Гордиюк

Генетические и эпигенетические изменения
в клетках злокачественных опухолей урогенитальной сферы человека

Резюме

Более 90 % злокачественных новообразований у человека имеют эпителиальное происхождение. Рак органов урогенитальной сферы представляет серьезную проблему в связи с его распространенностью и высоким показателем смертности. Образование опухолей обусловлено различными повреждениями генетического аппарата клетки, а также эпигенетическими факторами (пе- рестройки хроматина при модификациях гистонов, регуляция экспрессии генов с участием некодирующих малых РНК, нарушение процессов метилирования ДНК). В обзоре проанализированы генетические и эпигенетические изменения при раке органов урогенитальной сферы.

Ключевые слова: рак урогенитальной сферы; модификации гистонов, метилирование ДНК, онкогены, мутации.

В. В. Гордіюк

Генетичні та епігенетичні зміни у клітинах злоякісних пухлин урогенітальної сфери людини

Резюме

Більше 90 % злоякісних новоутворень людини становлять пухлини епітеліального походження. Рак органів урогенітальної сфери є значною проблемою через свою розповсюдженість і високий показник смертності. Виникнення пухлин обумовлено різними пошкодженнями генетичного апарату клітини, а також епігенетичними факторами (перебудови хроматину при модифікаціях гістонів, регуляція експресії генів за участі некодуючих малих РНК, порушення процесів метилювання ДНК). В огляді проаналізовано генетичні та епігенетичні зміни при раку органів урогенітальної сфери.

Ключові слова: рак урогенітальної сфери, модифікації гістонів, метилювання ДНК, онкогени, мутації.

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