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Genetic and epigenetic changes of genes on chromosome 3 in human urogenital tumors

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Numerous disorders of genes and alterations of their expression are observed on a short arm of human chromosome 3, particularly in 3p14, 3p21, 3p24 compact regions in epithelial tumors. These aberrations affect the key biological processes specific for cancerogenesis. Such genes or their products could be used for diagnostics and prognosis of cancer. Genetical and epigenetical changes of a number of genes on chromosome 3 in human urogenital cancer, their role in cellular processes and signal pathways and perspectives as molecular markers of cancer diseases are analyzed in the review.

Keywords: human chromosome 3, tumor suppressor genes, DNA methylation, microRNA, urogenital cancer, molecular oncomarker.

The process of malignization is promoted by genetic and epigenetic changes, affecting different chromosomes to a certain degree. Numerous chromosome aberrations (for instance, loss of heterozygosity) as well as decrease in the expression of many genes due to hypermethylation of promoters, histone modifications, alternative splicing of transcripts or disorders of protein translation by microRNA are observed on the short arm of human chromosome 3 in cells of tumors of epithelial origin.

Deletions on arm 3p are related to the most frequent changes in the majority of tumors of epithelial origin. These aberrations were observed in 90 – 100 % of cases of renal clear cell carcinoma (RCC) and cervical carcinoma (CC), and were significantly present in ovarian cancer (OC) and prostate cancer (PC) [1, 2]. Amplifications of genes of chromosome 3 play an important role in malignization of urogenital organs [3]. Satellite DNA and retrotransposons condition the presence of duplications on the short arm of human chromosome 3, promoting carcinogenesis [4]. Monosomy and polyploidia of chromosome 3 also promote the development of urogenital malignant neoplasms, for instance, CC [5].

Epigenetic and genetic disorders in the regulation of the level of expression of some genes of human chromosome 3 in tumor cells will be discussed later, in the analysis of aberrations of its specific region.

"Topography" of genes on chromosome 3 and cancer. The highest number of genes of human chromosome 3, susceptible to changes in urogenital tumors, is located in the compact regions 3p14, 3p21, and 3p24.

Thus, there is evident considerable percentage of deletions in locus 3p14.1-3p14.2 [6] and decrease in expression in RCC for fragile histidine triad gene (*FHIT*), 3p14.2 [7]. Hetero- and homozygous deletions of *FHIT* gene may result in disorders in the processes of DNA replication in cells [8]. The development of renal carcinoma (RC) is also related to the translocations of microphthalamia-associated transcription factor

(*MITF*) gene, 3p14.2-p14.1 [9]. OC is characterized by the loss of heterozygosity in the region 3p14 [10] and hypermethylation of *FHIT* [11]. The decrease in the expression of genes *FHIT* and *ADAMTS9* (ADAM metallopeptidase with thrombospondin type motif 9, 3p14.1) increases the risk of PC [12, 13]. The decrease in the expression of *FOXP1* (forkhead box P1, 3p14.1) [14] and specific deletion, resulting in the formation of chimeric gene [15], are also observed in this oncopathology. At the early stages of CC there were observed deletions [16], hypermethylation and loss of expression some genes in locus 3p14.2 [17]. The results of research with *NotI*-microarray show methylation/ deletions of genes *FOXP1* and *MITF* in this region in urogenital tumors [18, 19].

Inactivation of the cluster of about 20 potential genes – suppressors of tumor growth of region 3p21.3, affects the course of key biological processes, determining the specificity of carcinogenesis [20], therefore, these genes may be used as biomarkers for diagnostics and prognosis of oncological diseases [21].

The methylation of promoters of genes *RASSF1A* (Ras association domain family member 1, 3p21.3) [22] and *LTF* (lactotransferrin, 3p21.3) [23] is revealed in PC. The methylation of *RASSF1A* [24] and *TU3A* (3p21.1) [25] as well as high percentage of deletions in the region 3p21.3, in particular, for gene *NPRL2* (nitrogen permease regulator-like 2) were found in RC [26]. This oncopathology is also characterized by the loss of heterozygosity and hypermethylation of gene *MLH1* (mutL homolog 1, colon cancer, nonpolyposis type 2, 3p21.3) [27, 28]. The effect of aberrations of telomeric 3p21.3T and centromeric 3p21.3C regions, for instance, deletions of gene *DLEC1* (deleted in lung and esophageal cancer 1, 3p21.3), is observed in CC [29]. This disease is related to hypermethylation of genes *BLU* (3p21.3), *RASSF1A* [30] and deletions in *NPRL2* [26]. The development of OC is promoted by hypermethylation of the CpG regions of genes *MLH1* [31] and *DLEC1*. The decrease of *DLEC1* expression is also connected with hypoacetylation of histones [32].The decrease in expression of genes *RIS1* (Ras induced senescence 1, 3p21.3) and *HEG1* (3p21.2) [33] as well as hypermethylation of promoter of gene *RASSF1A* [34] were demonstrated for serous ovarian cancer. A considerable decrease in expression of HYAL1 (hyaluronoglucosaminidase 1, 3p21.3) and, therefore, anomalous accumulation of hyaluronan, tumorigenic polysaccharide, in extracellular matrix [35] were also observed at this pathology.

The data, obtained with of *NotI*-microarrays, demonstrate genetic/epigenetic changes in cancer of urogenital organs in the 3p21.3 region for genes *ITGA9* (integrin, alpha 9), *RBSP3* (RB protein serine phosphatase gene on chromosome 3) and *GNAI2* (guanine nucleotide binding protein, alpha inhibiting activity polypeptide 2) [18, 19].

Considerable disorders were observed in the 3p24 region of chromosome 3 in urogenital tumors. For instance, the loss of heterozygosity was observed in locus 3p24.2 in RC [36], deletions were found in CC [37] and OC [10], point mutations and loss of heterozygosity of *THRB* (thyroid hormone receptor, beta, 3p24.2) – in PC [38]. The increase in expression of one of antiapoptotic gene IL-17RL forms (interleukin-17 receptor-like protein, 3p25.3-3p24) due to alternative splicing was also observed for this pathology [39]. In PC the deletions in loci 3p24 and 3p22 are found in more than half of patients [40]. The results of *NotI*-microarray demonstrate methylation/ deletions in urogenital tumors in the 3p24 region for genes *RPL15* (ribosomal protein L15), *RARbeta* (retinoic acid receptor, beta), *LRRC3B* (leucine rich repeat containing 3B), *SH3BP5* (SH3-domain binding protein 5), and *THRB* [18, 19].

Urogenital malignant neoplasms are known for aberrations in the region 3p25-3p26. For instance, the loss of heterozygosity was revealed in CC in loci 3p26.1-3p25.2 [41]. Deletions 3p25-3p26 were found in OC [10] and RC [42]. Some authors revealed the connection between disorders in locus 3p25-3p26 and the risk of developing PC [43]. The data of *NotI*-microarray demonstrate changes in the region 3p25-26 in cancer of urogenital sphere for genes *BHLHB2* (basic helix-loop-helix domain containing, class B, 2), *WNT7A* (wingless-type MMTV integration site family, member 7A), *VHL* (von Hippel-Lindau tumor suppressor), and *MINT24* [18, 19].

Besides, the gene of histone deacetylase HDAC11 with the locus CpG in promoter site was localized in the 3p25 region [44]. This enzyme regulates the expression of interleukin-10 and thus – the processes of

inflammation and immune response [45]. Inactivation of HDAC11 in cancer may testify to its tumor-suppressing features.

Genetic aberrations on the long q arm of human chromosome 3 are significantly present in CC and are most frequent in the 3q21 region [46]. The increase in expression of gene *EVI1* (ecotropic viral integration site 1,3q26), destroying normal duplication of centrosomes, is also related to the risk of CC development. The product of this gene interacts with histone methyl-transferases, promoting immortalization of tumor cells [47]. 100% of investigated samples of invasive CC show amplifications of *TERC* (telomerase RNA component, 3q26), which is also required for immortalization [48].

A compact region is revealed inside the 3q21 region, containing potential tumor-suppressing genes and oncogenes, associated with OC and RC [20]. Gene *PIK3CA* (phosphoinositide-3 kinase, catalytic alpha polypeptide, 3q26) is amplified in OC [49]. PC is characterized by amplifications of genes *IL12A* (interleukin 12A, 3q25-3q26), *SOX2* (SRY (sex determining region Y)-box 2, 3q26-q27), *MDS1* (myelodysplasia syndrome 1, 3q25-3q27) [50], and *TLOC1* (translocation protein 1, 3q26.2) [51].

The results of *NotI*-microarray[s] demonstrate the disorders in q arm of human chromosome 3 in cancer of urogenital organs for genes *GATA2* (GATA binding protein 2), *RAP2B* (member of RAS oncogene family), *FGF12* (fibroblast growth factor 12), *TRH* (thyrotropin-releasing hormone) and *SOX2* [18, 19].

Therefore, the relation to tumor formation in urogenital sphere was first revealed for some genes of human chromosome 3 and confirmed for others using the research with *NotI*-microarrays. In particular, these data were obtained for gene *GNAI2*, the decrease in expression of which was previously revealed in OC [52], for *RARB*, hypermethylated and capable of losing heterozygosity in CC [53, 54], for *RBSP3*, which is susceptible to deletions in this pathology and decreases the expression [55]. The data of inactivation due to hypermethylation of promoter or mutations in RCC [56] also coincide with the data of *NotI*-microarray for gene *VHL*.

MicroRNAs, the genes of which are localized on chromosome 3, deserve special attention. It is noteworthy that disbalance in expression of microRNA in cancer, including urogenital organs, may be conditioned by both genetic and epigenetic mechanisms [57]. The progression of prostate cancer is related to the decrease on the level of miR26a (3p22.2), which is a regulator of immune response and apoptosis [58]. The expression of miR135a (3p21.1) also changes in PC [59]. In RCC there is a sharp drop in the expression of miR135a and miR-28 (3q28) [60]. Changes in gene *mir-191* (3p21.31) are associated with OC [61]. The disorder of expression of miR-191, miR-28, miR-425 (3p21.31) and let-7g (3p21.1) is remarkable for CC [62]. Similarly to the protein-coding genes, suppressors of tumor growth, the genes of microRNA tend to cluster in specific regions of chromosomes [63].

The largest number of microRNA genes of human chromosome 3, the changes in expression of which were revealed in urological tumors, is concentrated in the 3p21 region. This region is the subject to deletions, in RCC, in particular [60].

Functions and participation in signaling of gene products of chromosome 3. The specificities of changes in a number of genes of human chromosome 3 and proteins, coded by them in urogenital malignant neoplasms, are presented in Table. According to the literature data, genetic/epigenetic aberrations or disorders in expression of definite genes were found only in urogenital malignant tumors. However, the changes in many genes are associated with different tumors of epithelial origin as well as with malignant neoplasms of other nosological types. These genes either belong to known/potential tumor suppressors or are oncogenes. Proteins, coded by them, participate in the regulation of cellular cycle, cell differentiation and apoptosis. They are presented by transcription factors, growth factors/cytokines, receptor proteins, and enzymes.

Some genes of human chromosome 3 demonstrate opposite features in different types of malignant neoplasms. For instance, as stated above, the decrease in expression is remarkable for transcription factor *FOXP1* in epithelial tumors. On the contrary, in lymphoma *FOXP1* acts as an oncogene due to translocations [64].

The identification of signaling pathways, their key elements and corresponding aberrations in tumor

Ways of inactivating genes of human chromosome 3 in malignant neoplasms and functions of proteins, coded by them

Gene	Regulation/change in expression	Tumor localization	Functions of protein, cellular processes	Reference
MINT24	Methylation/deletions	Kidneys, ovaries, cervix uteri, large intestines	Unknown	[18], [19]
BHLHB2	Methylation/deletions	Cervix uteri, ovaries, pancreatic gland	Transcription factor, cell differentiation, apoptosis	[18], [19]
ITGA9	Methylation/deletions	Cervix uteri, ovaries, lungs	Glycoprotein, adhesion	[18], [19]
NKIRAS1	Methylation/deletions	Cervix uteri, skin, stomach	Apoptosis	[18]
RARbeta	Methylation/deletions	Kidneys, cervix uteri, ovaries, esophagus, liver, leukemia	Cell differentiation, apoptosis	[18], [19]
RBSP3	Methylation/deletions	Kidneys, cervix uteri, ovaries, lungs	Phosphatase, regulation of cellular cycle	[18], [19]
VHL	Methylation/deletions, mutations	Kidneys, cervix uteri, ovaries, mammary gland, pancreatic gland, leukemia	Ubiquitinylation, apoptosis, angiogenesis	[18], [19]
WNT7A	Methylation/deletions	Cervix uteri, lungs, pancreatic gland, neuroblastoma	Signaling protein, embryogenesis, adhesion, cell differentiation	[18]
FOXP1	Methylation/deletions	Kidneys, ovaries, cervix uteri, prostate, rectum, lymphoma	Transcription factor, ontogenesis	[14], [15], [18]
LRRC3B	Methylation/deletions	Kidneys, ovaries, cervix uteri, stomach and large intestine, leukemia	DNA reparation, cell proliferation	[18], [19]
GATA2	Methylation/deletions	Ovaries, prostate gland, leukemia	Transcription factor, hematopoiesis	[19]
FGF12	Change in expression, methylation/deletions	Nasopharynx/thyroid gland, ovaries	Factor of growth of fibroblasts, angiogenesis	[19]
RAP2B	Increase in expression, methylation/deletions	Lungs/ovaries	Small GTPhase	[19]
MITF	Translocations, methylation/deletions	Melanoma, kidneys, ovaries	Transcription factor, cell differentiation	[9], [19]
TRH	Increase in expression, methylation/deletions	Melanoma/ovaries	Autocrine growth factor	[19]
SOX2	Methylation/deletions	Ovaries, prostate gland, lungs, stomach, glia	Transcription factor, cell cycle, apoptosis	[19]
THRB	Methylation/deletions, mutations	Neuroblastoma, thyroid gland, liver, kidneys, ovaries	Receptor of thyroid hormone	[19], [38]
GNAI2	Methylation/deletions, decrease in expression	Kidneys, ovaries	Receptor protein G	[19]
SH3BP5	Methylation/deletions, decrease in expression	Cervix uteri, mammary gland	Signaling protein, growth and differentiation	[18]
MLH1	Gene methylation and dimethylation of histone H3	Gastrointestinal tract, prostate, ovaries	Apoptosis	[27], [28]

Окончание таблицы

Gene	Regulation/change in expression	Tumor localization	Functions of protein, cellular processes	Reference
NPRL2	Deletions	Kidneys, cervix uteri, lungs	Proliferation	[26]
ADAMTS9	Methylation, decrease in expression	Nasopharynx, prostate gland	Adhesion	[13]
HIAL1	Decrease in expression	Ovaries	Enzyme	[35]
TERC	Amplification	Cervix uteri	Immortalization	[48]
EVI1	Amplification; increase in expression	Prostate gland; cervix uteri, leukemia	Remodeling of chromatin	[47]
TLOC1	Amplification; increase in expression	Prostate gland	Ubiquitinylation	[51]
IL12A	Amplification	Cervix uteri; prostate gland	Cytokine	[50]
PI3KCA	Amplification	Ovaries	Kinase, proliferation	[49]

formation is extremely important for understanding carcinogenesis in general and the development of specific types of cancer. Many products of genes of chromosome 3, the relation of which to cancer of urogenital sphere is well-known, either are components of signaling cascades or affect their functioning.

A classic example of this fact is kinase PIK3CA. Via signaling pathway PIK3/Akt an estrogen regulates the expression of HIF1alpha, the key factor of invasion and metastasis, which was shown for OC, in particular [65]. The role of *VHL* in inhibition of expression of HIF1alpha is known [66]. According to the recent data, tumor-suppressing microRNA, coded by genes of chromosome 3, e.g. miR135a, participate in the regulation of response to hypoxia in RCC [60].

The products of genes *VHL* and *NKIRAS1* regulate in different ways the activity of signaling cascade with the participation of NF-kappa B, which realizes its anti-apoptotic features in transformed cells, when activated with protein Ras [67]. Parallel inactivation of *VHL* and *RASSF1A* was revealed in RCC, which may testify to synergism of activity of these tumor-suppressing genes [68]. It is known that *RASSF1A* participates in the regulation of signaling pathways together with Erk [69].

The signaling pathway WNT7A/catenin beta is required for cell adhesion [70]. Besides, via activation of JNK-pathway WNT7A induces the expression of cadherins and cell differentiation. In its turn, the product of gene *SH3BP5*, protein sab, regulating the level of expression of BTK (Bruton tyrosine kinase) and probably playing the role of a switch between JNK- and BTK-signaling pathways in mitochondria, is a target for JNK and SAPK3 [71].

Protein RBSP3 promotes the functioning of signaling pathway of retinoblastoma due to dephosphorylation of RB1 [72]. Protein SOX2, a structurally important component of Golgi apparatus, which is likely to induce apoptosis with caspase 3 and GRASP65, participates in the regulation of this pathway too [73].

Oncogene *BRAF* regulates the transcription of *MITF* via ERK and accelerates degradation of *MITF* by ubiquitin-proteosome pathway [74]. The product of *LTF* gene participates in the regulation of MAPK and promotes the termination of cellular cycle [75].

Protein FHIT serves as a target for protein-kinase Src, modulating the signaling pathway Akt-survinin [76]. On the other hand, the product of gene *NPRL2* is a negative regulator of signaling pathway Src/PDK1 (3-phosphoinositide-dependent protein kinase-1), required for proliferation [77]. Protein FOXP1, a target for androgen and its receptor in PC, participates in the signaling pathways of hormone-dependent tumors [78].

Cytokine IL-12 causes the induction of interferon gamma, participates in differentiation of Th1 and Th2, and activates transcription factor STAT4 [79].

MicroRNA let-7g is involved in the signaling cascade, affecting the capability of tumors to metastasis [80]. Oncogene *myc* is capable of inhibiting the expression of miR26a in cancer and, therefore, controlling the level of interferon beta [81].

It is noteworthy that signaling pathways, involved in the development of a tumor of the same organ, may change depending on histological specificities, as it was shown for different subtypes of OC [82].

A more detailed analysis of participation of products of genes, discussed in the review, in the signaling pathways of cells with the consideration of known complicated interactions, which vary in different types of cancer, is well beyond the frame of current work. Nevertheless, it is evident that human chromosome 3 is an important object for study of carcinogenic processes as well as for determination of genes - tumor suppressors and potential oncomarkers of cancer diseases, including malignant neoplasms of urogenital sphere.

Chromosome 3 and molecular oncomarkers. At present there is an active search for molecular oncomarkers, including epigenetic ones, which may be used for prediction of tumor behavior, for instance, probability of metastasis and resistance to medical preparations as well as for timely diagnostics.

The possibility of early diagnostics and prognosis of the disease course is investigated for urogenital malignant neoplasms. Epigenetic regulation of a number of genes is a frequent cause of decreased resistance to medicine for cancer, OC in particular [83].

At early stages of CC the monosomy and polyploidy of chromosome 3 can be potential oncomarkers [5]. This pathology has evident hypermethylation and loss of heterozygosity in tumor suppressors of chromosome 3 – *VHL*, *FHIT*, *RARB*, *RASSF1A*. The decrease in the expression of *RASSF1A* was considered as prognostic factor due to the mentioned aberrations [54].

Besides, the degree of methylation of promoter *RASSF1A* correlates with the progression of RCC [24]. The aggression of RC [84] and PC depends on the level of *TERC* expression. The increase in *TERC* expression in prostate cancer corresponds to the increase in the degree of differentiation by Gleason and the level of PSA (Prostate Specific Antigen) in blood serum of patients [85]. The expression profile of microRNA is also suggested for diagnostic and prognostic purposes in PC, in particular, for evaluation of probability of relapse after prostatectomy [86].

The methylation of promoter of gene *MLH1* results in sharp increase in OC progression [87]. Hypermethylation of GC-rich clusters of ribosomal genes is also revealed for this oncopathology [88]. Poor survival for OC is related to the amplification of gene *EVI1* [89].

Despite the fact that the methylation of CpG-loci is remarkable for carcinogenesis in general, the picture of methylation is specific for each type of tumors [90]. Besides, it may change within one localization depending on the clinical stage of disease (for instance, the degree of methylation of promoter *RASSF1A* increases with progression of RCC) [68] and on the histological subtype of the tumor (for instance, changes in the methylation status of genes in serous, mucinous and clear cell renal carcinoma are different) [91]. The profile of gene expression also changes with tumor progression. The sets (signatures) of genes with aberrant expression in cancer are unique for each histological subtype within one type of tumors. On the contrary, similar signatures are alike for different malignant neoplasms with close histological structure, which is notable for RCC and clear cell OC [92]. This specificity should be considered while analyzing the sets of corresponding markers.

As the profiles of expression of microRNAs were also found to be specific for different histological subtypes within one localization, it was suggested to use the panels of microRNAs, in particular, for molecular classification of renal tumors [93].

In clinical conditions a possibility of revealing molecular oncomarkers in biological liquids of the organism is extremely important, as it simplifies the diagnostic process significantly. The latter is absolutely true regarding malignant neoplasms of urogenital organs.

Gene *ACPP* (prostatic acid phosphatase, 3q21–3q23) codes a protein, the amount of which in blood of patients with PC increases considerably compared to hyperplasia [94]. It was also shown that in case of PC the level of microRNA in blood serum may serve as a marker of response to chemotherapy [95]. It

is suggested to conduct early diagnostics of PC by determining aberrant methylation of promoters of genes in the patients' samples, taken for Papanicolaou test [96].

In case of OC, blood samples reveal changes in the methylation of gene *RASSF1A* on stage I with the specificity of 100% and sensitivity of 82% [33]. The profile of microRNAs, determined in the patients' blood, is also used for OC screening [97].

It should be noted that hypermethylation of *RASSF1A* gene in RC, PC, and CC may be an important indicator for early tumor detection in blood serum or urine [22]. The analysis of methylation profile of DNA, related to the surface of blood cells, e.g. *RARbeta2* fragments, seems to be promising for early diagnostics of cancer [98].

The research of genetic and epigenetic (cancer specific epigenetic fingerprint) specificities in each definite case of malignant neoplasms using novel technologies reveals new perspectives for clinical diagnostics of early stages of oncological diseases, evaluation of their possible development and cancer therapy. The implementation of large-scale international projects, including Human Epigenomic Project [99], will undoubtedly promote the introduction of achievements of molecular biology into medical practice.

В. В. Гордиюк

Генетические и эпигенетические изменения
генов 3-й хромосомы человека в клетках
опухолей урогенитальной сферы

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Резюме

На коротком плече 3-й хромосомы человека, особенно в компактных участках 3p14, 3p21 и 3p24, в клетках опухолей эпителиального происхождения наблюдается значительное количество нарушений генов и изменение их экспрессии. Эти аберрации влияют на протекание ключевых биологических процессов, определяющих особенности канцерогенеза. Такие гены или их продукты могут быть использованы для диагностики и прогноза течения онкологических заболеваний. В обзоре проанализированы генетические и эпигенетические изменения ряда генов 3-й хромосомы человека при раке органов урогенитальной сферы, их роль в клеточных процессах и сигнальных путях, а также перс- пективы применения в качестве молекулярных онкомаркеров.

Ключевые слова: 3-я хромосома человека, гены – супрессоры опухолей, метилирование ДНК, микроРНК, рак урогенитальной сферы, молекулярные онкомаркеры.

В. В. Гордіюк

Генетичні та епігенетичні зміни генів 3-ї хромосоми людини
у клітинах пухлин урогенітальної сфери

Резюме

На короткому плечі 3-ї хромосоми людини, особливо на компактних ділянках 3p14, 3p21 і 3p24, у клітинах пухлин епітеліального походження спостерігається значна кількість порушень генів та змін їхньої експресії. Подібні аберації впливають на проходження ключових біологічних процесів, які визначають особливості канцерогенезу. Такі гени або їхні продукти можна використовувати для діагностики і прогнозування перебігу онкологічних захворювань. В огляді проаналізовано генетичні та епігенетичні зміни низки генів 3-ї хромосоми людини при раку органів урогенітальної сфери, їхня роль у клітинних процесах і сигнальних шляхах, а також перспективи застосування як молекулярних онкомаркерів.

Ключові слова: 3-я хромосома людини, гени – супресори пухлин, метилювання ДНК, мікроРНК, рак урогенітальної сфери, молекулярні онкомаркери.

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