Molecular-Genetic And Cytogenetic Characteristics Of Sporadic Kidney Cancer

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Abstract
To compile this literature review, we studied at least 100 publications devoted to the genetic basis of clear cell, papillary, and chromophobic sporadic kidney cancer pathogenesis. Each of them considered the role of somatic gene and chromosomal mutations in the initiation, promotion, and tumor progression of sporadic RCC, emphasized the importance of determining the mutagenic profile of RCC for the future of patients.

Keywords: sporadic renal cell carcinoma, damage to the genes of VHL, BPRM-1, BAP-1, SETD-2, RASFF-1, FHIT, etc.

Introduction
Nowadays, kidney cancer remains one of the most significant medical and social problems. Over the last 8 years prevalence of KC has increased in 1,63 times in Russia (by 38,77%) – from 78,5 patients among 100 000 people in 2011 to 128,2 in 2019. Annual growth of this index was 5,94% on average. In 2019, kidney cancer took the 7th position by its frequency. In the register of malignancies including 24 positions, the higher positions were taken by tumors of lymphatic and hematopoietic systems, colon, prostate gland, uterus body, skin and mammary gland. Demand in specialized medical aid for kidney cancer increased in the same degree [Kaprin A.D. et al., 2020].

The term “kidney cancer” denotes a heterogeneous group of tumors of renal tubule epithelium that includes different histogenetic variants of sporadic (97-98%) and hereditary (2-3%) malignancies [Mikhalenko D.S., 2008].
Morphological forms of sporadic renal cell cancer (RCC) are clear-cell RCC (cc RCC, clear cell carcinoma, ≈70-75% of cases); papillary and chromophobic RCC (pRCC and ch RCC, ≈10-15% and ≈5% of cases, respectively); as well as occasional oncocytoma; Bellini duct carcinoma; medullary carcinoma; RCC with translocation TFE3; neuroblastoma-associated renal cell carcinoma; mucinous tubular and spindle cell carcinoma; follicular carcinoma. Rare variants of RCC listed above account not more than 5% of all the RCC cases [Braga E.A. et al., 2016]. Pathogenesis of all sporadic RCC forms is based on admitting renal tubule epitheliocytes with damaged DNA into mitosis and further proliferation of the damaged cells.

It’s worth noting that in terms of contemporary medical science it’s more correct to mention only exogenous risk factors of DNA alteration, but not particular causes of this kind of damage. The risk factors include smoking, obesity, hypertension, long affect of trichlorethylen [Chow W.H. et al., 2010; Welch H.G. et al., 2010; Li P. et al., 2015]. The objects of damaging impact are proto-oncogenes regulating mitotic division of healthy cells (for instance, VHL, BPRM-1, BAP-1, SETD-2, RASFF-1, FHIT, etc.), alteration results – gene and/or chromosome mutations.

In clear cell carcinoma (the name is related to clear or eosinophilic cell cytoplasm composing the tumor substrate), the main molecular-genetic and cytogenetic disorders are deletions in the short arm of chromosome 3 and 9, increase of chromosome 5 copies and biallelic inactivation of gene VHL, as well as less frequent mutations of genes PBRM1, BAP1, SETD2, KDM5C, KDM6A and very rare mutations of genes TP53, RB1, BRAF, EGFR, ERBB2 [Choueiri T.K. et al., 2013].

Proto-oncogene VHL is localized in the short arm of chromosome 3. The product of its expression is protein VHL that together with protein CUL2, elongin-D and elongin-C forms a specific multiprotein complex, and in terms of normoxia it is involved in proteasome degradation of α-subunit of heterodimer protein HIF1 (HIF1 – hypoxia-inducible factor, transcriptional protein) previously hydroxilated with enzyme prolylhydroxilase [Audenet F. et al., 2011; Bader H.L., et al., 2012]. Due to this, in terms of normoxia, HIF-1 formation is blocked and realization of its effects is excluded [Portnichenko V.I. et al., 2012; Semenza G.L., 2009; Myllyharju J. et al., 2013]. In cases of oxygen deficiency in tissues, hydroxylation and destruction of HIF-1-α don’t take place. HIF-1 is accumulated in cell nuclei resulting in expression of erythropoietin genes, vascular endothelial growth factor (VEGF), glycolytic enzymes, stimulators of cell proliferation, which is the basis of long-term adaptation to hypoxia [Pavlov A.D. et al., 2011; Zagorska A. et al., 2004; Qingdong K., 2006; Sendoe A. et al., 2010].

In molecular-genetic and cytogenetic investigations, inactivating mutations of gene VHL (deletion, insertion, missense mutations) are revealed in 50-80% of sporadic clear cell carcinoma cases. The consequence of the noted chromosome, gene and local changes is the impairment of proteasome degradation of α-subunit of transcriptional protein HIF1 with accumulation of HIF1 in the nucleus of the damaged cell and stimulation of cell proliferation and angiogenesis [Rechsteiner M.P. et al., 2011; Arjuman W. et al., 2012].

30-40% of patients with sporadic clear cell carcinoma have somatic point inactivating mutations of gene BPRM-1 arising apart of damage / non-damage of gene VHL. Biological significance of BPRM-1 is determined by the function of protein BAF-180 expressed by this gene. The latter is a subunit of a specific module in complex of PBAF being a member of SWI/SNF family (one of the four families remodeling chromatin) [Sheinov A.A. et al., 2019; Clapier C.R. et al., 2009; Thompson M., 2009; Roy D.M. et al., 2014]. The result of remodeling can be both
activation of chromatin and obtaining an access for transcription apparatus to particular DNA areas and its inactivation. Specific action of BAF-180 as a part of PBAF consists in forming the inactive structure of chromatin due to binding lysine remains (acetylated under SWI/SNF effect) in histone “tails”, which predetermines tumor-suppressing character of BPRM-1 and BAF-180 function [Brownlee P.M. et al., 2012]. This function is lost on extended deletions in the short arm of chromosome 3 (where BPRM-1 is localized) or point mutations of gene BPRM-1. According to S.J. Nam et al. (2015) who performed molecular-genetic investigations of 657 patients with clear cell renal carcinoma, presence of decreased expression of BPRM-1 statistically correlates with the patients’ elderly age, enlarged size of the neoplasm, a higher stage of the process and a lower degree of cell differentiation comprising the tumor substrate, worse indices of oncospecific survival compared to those in patients with sporadic cc RCC conditioned by inactivation of gene VHL without BPRM-1 damage [Nam S.J. et al., 2015].

About 10% of patients with sporadic cc RCC are registered to have inactivating mutations of tumor suppressor-gene BAP-1, localized on the long arm of chromosome 3 [Keefe S.M. et al., 2013]. The expression product of this gene is protein BAP-1 having 3 domains. One of them is enzyme ubiquitin carboxy-terminal hydrolase (UCH). UCH function is participation in ubiquitin-dependent proteolysis of various protein structures in a large amount that have performed their function or are damaged (a kind of cytoplasmic “biological litter” of protein origin capable to interfere negatively into the processes of cell cycle regulation and/or alter the activity of different signaling pathways thus creating the conditions for tumor cell transformation). There are two stages of ubiquitin-dependent proteolysis: the first one is when ubiquitin molecules are covalently attached to the protein to be degraded; the second one involves the cleavage of the unwanted protein in proteasome. The enzyme UCH is a participant of the second stage, separating ubiquitin from ubiquitinated proteolysis units [Zadvorov A.A. et al., 2017; Komander D., 2009; Kimura Y. et al., 2010]. Thus, damage of gene BAP-1 and its decreased expression results in disorders of degradation of proteins, cell cycle, differentiating processes, signaling pathways functioning. Due to this, on inactivation of gene BAP-1 there appear high risks of developing malignancies and high risks of their metastasis [Amaro A., 2017].

In 8-15% of sporadic ccRCC cases (according to Nemtsova M.V. et al., 2017) one of the causes of developing a tumor is damage of gene SETD-2 associated with decrease / absence of protein SETD-2 expression – histone methyltransferase, covalently trimethylating lysine 36 histone H3 in nucleosomes [Nemtsova M.V. et al., 2017]. Providing the reactions of histone H3 trimethylation determines the biological role of protein SETD-2: 1) in general, involvement in the processes of histone modification, being the most important mechanisms of epigenetic regulation of transcription; 2) in particular (supposedly), restoration of chromatin normal structure after transcription [Li F. et al., 2013; Carvalho S. et al., 2014]. Over the last years, there have appeared some messages about positive significance of SETD-2 and protein H3K36me3 (product of SETD-2-dependent trimethylation of lysine 36 histone H3) for the repair processes of the altered DNA. For instance, according to S. Carvalho et al. (2014), deficiency of gene SETD-2 expression results in failure to detect double-strand breaks of DNA at the checkpoint G1/S, as well as absence of signals to activate suppressor-gene p53 and induce apoptosis, to block DNA replication, to activate the repair processes of DNA. The consequence is admission of the cell with damaged DNA into mitosis [Carvalho S. et al., 2014].
Publications of Feng Li et al. (2013) show the significance of lysine 36 histone H3 trimethylate and, consequently, gene SETD-2 in realizing one of three mechanisms of excisional DNA repair - mismatch repair (MMR). Necessity of MMR is known to arise in the cases when during replication the daughter DNA strand is inserted with nucleotides, non-complementary to appropriate nucleotides in the parental strand (mismatch is erroneous pairs of nitrous compounds, such as guanine-thymine, guanine-guanine, adenine-cytosine, cytosine-cytosine). Besides, MMR mechanism is used in correcting interstrand crosslinks of CpG and other DNA damage induced by cisplatin, purine adductors of benzpyrene, aminofluorene derivatives, etc. Detection of mismatches is performed using the complex h Mut Sα consisting of homologous proteins hMSH2 + hMSH6 [Spivak I.M., 2006]. According to the findings of the investigation by Feng Li et al. (2013), protein H3K36me3 is necessary for recruiting the complex h Mut Sα (hMSH2 + hMSH6). The researchers emphasize the increased frequency of spontaneous mutations underlying the tumor growth on inactivation of gene SETD-2 and H3K36me3 deficiency [Feng Li et al., 2013]. Importance of SETD-2 and H3K36me3 for successful DNA repair, pathogenetic significance of negative SETD-2 mutations and the lost function of trimethylation of lysine 36 histone H3 are also confirmed by K.E. Hacker et al. (2016), R. Dronamraju et al. (2018), J. Li et al. (2019) and others [Kanu N. et al., 2015; Stone L., 2015; Giacci A.J., 2016; Hacker K.E. et al., 2016; Fahey C.C. et al., 2017; Dronamraju R. et al., 2018; Li J. et al., 2019].

In 2013 a group of researchers (A.A. Hakimi, I. Ostrovnaya, B. Reva and others) published the results of the multicenter study aimed at assessing the influence of suppressor-genes of malignant growth PBRM1, SETD2, and BAP1 (chromosome 3p21) on oncospecific survival (OSS) of the patients with clear cell renal carcinoma (n=609). According to the findings, in patients with ccRCC mutations of gene PBRM1 don’t exert any influence on OSS, however, as the researchers suggest, are the key factors of tumor initiation. On the contrary, having damaged genes SETD2 and BAP1 is associated with ccRCC progressing and OSS decline [Hakimi A.A. et al., 2013].

Nowadays, there is an established cause-effect relation between ccRCC development and progression and alteration of a number of genes controlling the signaling pathway PI3K/AKT/mTOR. Physiological function of PI3K/AKT/mTOR is participation in maintaining quantity and quality stability of the body cell composition due to regulation of proliferation and apoptosis processes.

The key “participants” of PI3K/AKT/mTOR-cascade are 1) lipid kinases phosphorylating 3-hydroxyl group of phosphoinositole and phosphoinositides (PI3-kinase); 2) serine-threonine protein kinase B (abbreviations – RKB or AKT have 3 domains: N – terminal PH domain, central catalytic and short C-terminal regulatory domains); 3) serine-threonine kinase from Pikk family (mammalian target of rapamycin, mTOR). The components of mTOR are two multidomain protein complexes - mTORC1 и mTORC2 [Papadimitrakopoulou V. et al., 2006; Engelman J.A., 2009].

Physiological activation of PI3K/AKT/mTOR occurs due to attaching the growth factors to the receptor tyrosine kinases. The latter provide localization of PI3-kinases A1 (PIK3CA) on cytoplasmic membrane. Then PIK3CA catalyzes phosphorylation of membrane phosphotidylinositole-4,5-biphosphate (PIP2) with formation of phosphotidylinositole-3,4,5-triphosphate (PIP3). Then AKT activation starts that is realized in the following way: firstly, PIP3 attaches to N-terminal PH domain AKT; secondly, - under the influence of phosphoinositide dependent kinase 1 (PDK1) and multidomain protein complex mTORC2, phosphorylation of...
catalytic domain by Thr308 and short C-terminal regulatory domain by Ser473. Activated AKT has an inhibiting effect of protein-activators of guanosine triphosphatase (GTP) for RHEB (Ras homologue enriched in brain). Hyperconcentration of RHEB becomes the activation factor of mTORC1 phosphorylating proteins p70S6K and 4EBP1, 4EBP2 and 4EBP3 with the functions of enhancing translation, ribosome biosynthesis and inhibiting mechanisms of cell death [Bader A.G. et al., 2005; Sarbassov D.D. et al., 2005; Shaw R.J. et al., 2006].

Besides, activated AKT is a stimulator of expression of gene MDM2 whose product – nucleus-localized E3-ubiquine-protein ligase MDM2 – detects and inhibits transcription of suppressor-gene p53 that is responsible for start of apoptic program in case of impossible DNA repair in the checkpoint G1/S [Murphy M. et al., 2019].

Adequate functioning of signaling cascade PI3K/AKT/mTOR is provided by various regulatory systems. The most investigated ones are 1) dephosphorylation of membrane phosphatidylinositole-3,4,5-triphosphate (PIP3) in phosphatidylinositole-4,5-biphosphate (PIP2) under influence of lipid phosphatase (expression product of gene PTEN located on the long arm of chromosome 10) prohibiting AKT activation [Keniry M. et al., 2008]; 2) AKT dephosphorylation in the short C-terminal regulatory domain by Ser473 (effector-compounds – protein phosphatases PHLPP1 and PHLPP2 coded by suppressor-gene PHLPP) [Gao T. et al., 2005]; 3) activation of GTP for RHEB under influence of TSC2-TSC1 complex and, therefore, inhibition of mTORC1 in terms of ATP hypoconcentration [Shaw R.J et al., 2004]; 4) absence of dephosphorylation of the key substrates mTOR S6K and 4E-BP1 in terms of hypoergosis related to the activation of gene REDD1 [Sofer A. et al., 2005].

All the compounds participating in evolving the signaling pathway PI3K/AKT/mTOR are the expression products of the corresponding (in most cases having the same name) proto-oncogenes and each of them can theoretically be a potential candidate-gene for developing sporadic ccRCC. However, in contemporary medicine, cause-effect relation between the damage of proto-oncogenes controlling PI3K/AKT/mTOR cascade and development of sporadic clear cell renal carcinoma as well as tumor progressing of this disease is proved only regarding to PIK3CA (1-3% cases of ccRCC), MTOR, TP53 and PTEN with frequency 6-7%, 1-2% and 5-7%, respectively [Nemtsova M.V. et al., 2017].

Sporadic papillary carcinoma (papillary renal cell cancer, p RCC) is diagnosed in 15-20% of patients with sporadic renal cancer [Nemtsova M.V. et al., 2017]. About 45% of patients with sporadic papillary carcinoma are registered to have multifocal character of malignant growth [Reutor V.E. et al., 2000]. There are two histological variants of p RCC. The substrate of type 1 tumors is presented by small cells with tiny nucleus and basophil cytoplasm having clusters of xantheme cells between them. Such variant occurs in about 70% of patients with p RCC. Cells of type 2 tumors are larger in size, there are nucleoli found in nuclei, cytoplasm is stained by acidic dyes [Ku J.H. et al., 2009].

Factors of tumor transformation and/or progression for sporadic p RCC type 1 can be somatic single activating mutations of proto-oncogene MET, as well as appearance of replicas of chromosome 7 and 17 in daughter cells [Courthod G. et al., 2015].

Proto-oncogene MET is localized on chromosome 7 in locus 7q21-31, its expression product is receptor tyrosine kinase (RTK) for tyrosine kinase receptors (TKR) of epitheliocytes of liver, pancreas and prostate gland, as well as kidneys, vessel walls, melanocytes. The most important biological role of RTK and, therefore, proto-oncogene MET is participation in paracrine
regulation of proliferative activity of the above cells [Wang K. et al., 2014]. The ligand for TKR is hepatocytes growth factor (HGF) that is formed in mesenchymal cells in an inactive form and after activation acquires the properties of a mitogenic stimulator. Binding with TKR, this ligand launches the process of sequential tyrosine autophosphorylation in all three domains of the receptor. Then it results in activation of signaling cascades MAPK, PI3K/AKT, STAT3 [Garcia-Guzman M. et al., 1997; Paumelle R. et al., 2002; Syed Z.A. et al., 2011].

During molecular-genetic and cytogenetic studies, the patients having p RCC, type 1, are registered to have missense mutations of gene MET (in about 10-20% of cases, according to the overall data) and/or amplification of locus 7q31 (in about 45% of cases). The consequence is excessive stimulation (overload) of the signaling pathways, which creates the conditions for admitting the cells with damaged DNA into mitosis [Kang X.L. et al., 2015].

Specific genetic alterations in p RCC, type 2, differ from those in p RCC, type 1. According to W.M. Linehan et al. (2016), the main events launching pathogenesis and/or tumor progression of papillary renal cell cancer of type 2 are epigenetic suppression of gene CDKN2A expression, mutations of gene SETD2 (their significance in pathogenesis of renal cancer was viewed above), formation of gene TFE3 chimeras, increased expression of the transcription factor of Nrf2-antioxidative response element (ARE) [Linehan W.M. et al., 2016].

In physiological conditions, gene CDKN2A localized on chromosome 9 encodes proteins p16 (inhibitor of cyclin-dependent serine/threonine protein kinases Cdk4 and Cdk6 providing cell promotion in S-phase in a complex with appropriate cyclins) and p14ARF (activator of suppressor-gene p53). The consequence of “stifling” CDKN2A is loss of p16 and p14ARF production, further disorders of cell cycle regulation with inactivation of “Check-point” mechanism in the check point G1/S and switching-off the mechanisms blocking the replication of the damaged DNA in S-phase [Zhao R. et al., 2016].

Gene TFE3 is located on chromosome X (locus Xp11.2). Its expression product is transcription factor E3 that is a member of transcription factors encoded by genes Mi TF, TFE3, TFEB and TFEC [Kuiper R.P. et al., 2004]. Biological role of E3 is determined by its participation in the regulation processes of transcription, life cycle and proliferative function of the cells. The result of chromosome Xp11.2 translocations can be fusion of TFE3 with other genes (the most known, PRCC, ASPL, PSF, Non O, CLTC) and formation of chimeric structures PRCC-TFE3, ASPL-TFE3, PSF-TFE3, NonO-TFE3, CLTC-TFE3 that act as active cell oncogenes in p RCC cancerogenesis and whose expression of transcription factor E3 noticeably exceeds that for wild-type TFE3 [Liu Y, et al., 2012].

Redox-sensitive Nrf2 transcription factor (nuclear E2-related factor 2) is a short-living protein degrading in human cells 15 minutes after its formation [Tkachev V.O. et al., 2011] having the function of controlling the expression of more than 500 ARE-dependent genes encoding biosynthesis of the enzymes of antioxidant defense system and the enzymes of II phase of xenobiotics detoxication [Chapple S.J. et al., 2012]. As B.M. Hybertson et al. (2012) note, being a part of redox-sensitive signaling system Nrf2/Keap1/ARE, “Nrf2 is “the main regulator” of antioxidant reaction…” that normalizes intracellular redox-homeostasis in hyperproduction and accumulation of reactive oxygen species in the cell [Hybertson B.M. et al., 2011]. On binding Nrf2 with DNA, antioxidant-response element (ARE) of DNA is used. Expression of Nrf2 is controlled by repressive protein KEAP1 having the function of Nrf2 ubiquination and degradation in 26S-proteosomes, as well as the function of regulation of Nrf2 transport into the nucleus and its binding
with DNA due to modification of Nrf2 amino acid remains [Pandey P. et al., 2017]. Besides, the factors regulating Nrf2 activity are also auxiliary components of Nrf2/Keap1/ARE system, such as gene CUL3 encoding biosynthesis of protein Cullin-3 with the function of polyubiquitination and further degradation of various protein substrates, including Nrf2 [Zenkov N.K. et al., 2019]. Elimination of KEAP1-repressive influence on Nrf2 becomes possible in case of modifying its sensitive thiol groups into electrophilic and/or oxidative compounds, including electrophilic metabolites of chemical carcinogenic factors and/or reactive oxygen species [Turpaev K.T., 2013; Jeddi F. et al., 2017].

Currently, there are 2 variants of Nrf2 participation in cancerogenesis of malignancies, including cancerogenesis of pRCC of type 2 [Kim J. et al., 2016; Menegon S. et al., 2016]. On the one hand, many researchers note that Nrf2/Keap1/ARE system can be described as a defense factor on the initiation stage of malignant growth in terms of effecting chemical and radiation carcinogenic agents [Jaramillo M.C. et al., 2013; Suzuki T. et al., 2013; Basak P. et al., 2017; Ngo H.K.C. et al., 2017; Li C. et al., 2018; Raghunath A. et al., 2018]; on the other hand, - as the most important element of inhibiting apoptosis and forming resistance of malignant cells to the action of specific anticancer drugs [Kim J. et al., 2016].

Hyperexpression of Nrf2 is observed in many malignancies (cancers of lung, head and neck, liver, esophagus, gall bladder, skin), there is a proof of its connection with somatic mutations of both the gene Nrf2 itself and the genes regulating its biosynthesis and activity [Shibata T. et al., 2008; Adam J. et al., 2011; Hu Y. et al., 2012; Ooi A. et al., 2013; Best S.A. et al., 2018; Kerins M.J. et al., 2018; Liu R. et al., 2018]. In sporadic pRCC, hyperexpression of Nrf2 is the most significant factor of tumor progressing and it arises because of somatic mutations of genes NRF2, CUL3, FH (encodes the enzyme fumarate hydrase, the result of FH inactivation is accumulation of intracellular fumarate, due to this inhibition of Keap1 and hyperexpression of Nrf2) and SIRT1 [Kinch L. et al., 2011; Ooi A. et al., 2013].

Sporadic chromophobic renal cell cancer (ch RCC) occurs in about 5% of sporadic RCC cases. More often the disease develops in patients aged 50-60. As a rule, fatal outcomes among the patients don’t exceed 10% [Dabbs D.J., 2006]. The tumor substrate consists of light polygonal cells (large ones, with wide cytoplasm or smaller ones with less cytoplasm) being a part of tubular-cystic structures or solid nests in edematic stroma. Hyperchromatic nuclei have irregular outline, presence of two nuclei is possible. There also exists eosinophilic chRCC variant that is characterized by susceptibility of tumor cell cytoplasm to acidic dyes.

Nowadays, genetic basis of sporadic chRCC pathogenesis is considered to be damage of genes TP53, PTEN, CDKN2A, NF2, as well as in some cases - BRAF и KRAS [Dolzhanskiy O.V. et al., ]. Inactivating somatic missense-mutations of suppressor-gene TP53 (located on the short arm of chromosome 17 in locus 17p13.1) occur in 32–42% of ch RCC cases with the frequency of 79% and 14% for sarcomatoid or carcinomatous tumor substrates, respectively [Oda H. et al., 1995; Cserni G. et al., 2002; Yang Y. et al., 2017]. According to C.F. Davis et al. (2014), about 9% of ch RCC patients have point mutations PTEN (chromosome 10, locus 10q23.31), 10% of patients – breaks in promotor region of gene TERT (chromosome 5, locus 5p15.33) [Davis C.F. et al., 2014].

Conclusion
Molecular-genetic damage underlies cancerogenesis of all the varieties of renal cell cancer. Diversity of their combinations is characteristic not only for a particular RCC type, but for each case in particular.

Scientific significance of molecular-genetic and cytogenetic investigations is undoubted for studying all the features of initiation, promotion and tumor progression of kidney malignancies on a molecular-genetic level. Even greater significance is attached to using these findings for individual therapy approach of sporadic renal cell cancer.

In contemporary medicine, target therapy of RCC includes inhibitors of receptor tyrosine kinases (soraphenib, sunitinib, axinitib, cabozantinib, lenvatinib), inhibitors of angiogenesis (pasopanid), monoclonal antibodies against circulating VEGF (bevacizumab, interferon-α), inhibitors of mTOR (temsirilimus, everolimus). However, effectiveness of these medicines remains a discussable issue [Nosov D.A., 2010].

Nevertheless, it appears evident that acquiring mutation tumor profile of each particular patient significantly increases accuracy of diagnosis verification and is a tool of determining potential targets for target pharmacological affect in terms of further effective scientific development of the problem.

References

16. Turpaev K.T. Signaling system Nrf2-Keap1. Regulation mechanism and importance for cell protection from toxic affect of xenobiotics and electrophilic compounds // Biochemistry. – 2013. – Vol. 78, № 2. – P. 147-166.
47. Jaramillo M.C., Zhang D.D. The emerging role of the Nrf2-Keap1 signaling pathway in cancer // Genes Dev. – 2013. – Vol. 27. – P. 2179-2191.


