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NF-KB AS A POTENTIAL PROGNOSTIC MARKER AND A CANDIDATE FOR TARGETED THERAPY OF CANCER

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The *NF-kB1* gene belongs to the family of transcription factors that are involved in the regulation of a wide range of biological reactions. It has been established that *NF-kB1* plays an important role in the regulation of immune responses, but more and more studies indicate that this gene is involved in the processes of oncogenesis and DNA repair. The product of this gene regulates the expression of genes involved in the development and progression of cancer. In recent years, numerous studies have been aimed at elucidating the functional consequences of the activation of *NF-kB1*, as well as its signaling mechanisms. In this regard, *NF-kB1* is an interesting therapeutic target for a possible personalized approach in the treatment of cancer. This article provides an overview of modern clinical studies of the *NF-kB1* gene, which acts as a predictive and prognostic marker in the treatment of cancer.
***Key Words*: *NF-kB1*, marker, personalized medicine, homologous recombination deficiency.**

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INTRODUCTION

The *NF-kB1* gene (nuclear factor kappa B subunit 1) is located on chromosome 4q24 and encodes the nuclear transcription factor NF-kB. It has a size of 156 thousand bp and consists of 24 exons separated by introns, the length of which varies in the range from 323 to 40 thousand bp [1]. The family to which this gene belongs includes five genes [2], however, it is the *NF-kB1* gene that, for almost two decades, has attracted the attention of researchers in many areas, which can be linked to its functions. The product of this gene specifically and quickly regulates an extensive spectrum of genes (over 500), plays a central role in immunological processes, etc. [3]. Despite the fact that the NF-kB1 protein was discovered by Rangen Sen and David Baltimore back in 1986 [4], it has only recently begun to be considered as a marker of treatment effectiveness in various malignant neoplasms [5]. Initially, it was considered to be a transcription factor, located only in B-lymphocytes, but later it was discovered to be present in all types of cells [6], also it has been proven to play a role in carcinogenesis, and its inhibition can lead to suppression of tumor development.

The main physiological function of NF-kB1 is to quickly reprogram the expression of a large set of genes (in particular proto-oncogenes) during infections, inflammation and some stressing effects. In addition, *NF-kB1* is involved in the inhibition of apoptosis, stimulation of angiogenesis, metastasis, increased cell survival and proliferative activity [7]. It has been shown that activation of *NF-kB1* is associated with tumor resistance to various therapeutic agents, as well as to radiation therapy [8]. It is important to note that normal level of *NF-kB1* expression is found in many types of malignant tumors, including breast cancer (BC), lung cancer, melanoma, etc. [8].

Clinical data indicate the prognostic value of *NF-kB1* in gastric cancer, since high expression of *NF-kB1* correlates with tumor size and a high likelihood of lymphogenous metastasis [9, 10]. In BC and ovarian cancer (OC), it was found that high content of NF-kB1 protein in tumor is associated with late clinical stage of the disease and a high degree of malignancy [11].

Of particular interest is the consideration of the transcription factor *NF-kB1* as a part of a homologous recombination deficiency (HRD) in patients with BC and OC, which is important for the effectiveness of chemotherapy in patients with these localizations [12–14]. In particular, it was found that in the absence of functional *BRCA1* or *BRCA2* genes, double-stranded DNA breaks cannot undergo repair by homologous recombination, and instead, repair can be carried out by activating alternative pathways of the *PARP1* and *NF-kB1* genes [15]. *BRCA1*-deficient tumor cells incapable of DNA repair exhibit high expression of nuclear *NF-kB1*. This leads to inhibition of apoptosis and the emergence of chemoresistance [16]. In the case of wild-type *BRCA1* being present in the tumor, it was shown that *NF-kB1* is involved in the resistance of tumor cells to DNA damaging agents [17].

Thus, to date, many experimental and clinical data have been accumulated that the *NF-kB1* gene plays an important role in the pathogenesis and progression of human tumors, which makes it a potential marker in the treatment of malignant tumors.

NF-KB1 ACTIVATION PATHWAYS IN NORMAL AND TUMOR TISSUE

Proteins NF-kB belong to a family of structurally related eukaryotic transcription factors that are involved

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Abbreviations used: BC – breast cancer; IKK – IκB kinase; HRD – homologous recombination deficiency; NEMO – NF-kB essential modifier; OC – ovarian cancer; PIDD – p53-inducible death domain-containing protein; RHD – Rel homology domain; RIP1 – receptor interacting protein 1.

in the control of a large number of normal cellular processes, such as immune and inflammatory reactions, cell growth and development and apoptosis. These transcription factors are persistently active in a number of pathological conditions, including cancer, arthritis, chronic inflammation, asthma, neurodegenerative diseases, and heart disease [18]. NF-kB1 is a heterodimeric complex of proteins of the Rel family, which in most resting cells are inactive and form comlexes with specific inhibitors — IkB in the cytoplasm [19]. The NF-kB/Rel family includes Rel (c-Rel), RelA (p65), RelB, NF-kB1 (p50) and NF-kB2 (p52 and its predecessor p100) [20]. Most members of this family, with the exception of RelB, can homodimerise and form heterodimers with each other [21].

The structure of Rel/NF-kB proteins began to be unveiled after molecular cloning of p50, which revealed that the N-terminal 300 amino acids were highly similar to the oncoprotein v-Rel, its cellular homologue c-Rel and the Drosophila protein Dorsal [22, 23]. This striking similarity led to this region being named the Rel homology domain (RHD) and cloning of the *RelA* cDNA demonstrated that it too contained an RHD [24]. Further studies added two more members to the mammalian Rel/NF-kB family, namely p52 (NF-kB2) and RelB, bringing the total to five [25]. The possibility that other members of this family exist was strengthened by the recent identification of a novel p50-related protein in B lymphocytes named p55;23 however, until a cDNA for this molecule is cloned it cannot be definitively ascribed to the Rel/NF-kB family [26].

The *NF-kB1* gene encodes a protein consisting of 969 amino acids with a molecular weight of 105 kDa, which was considered as a precursor of the p50 subunit of the NF-kB1 complex (Fig. 1) [27]. The product of the *NF-kB1* gene includes two subunits: p50, as well as IkBγ (an inhibitor of kBγ). The p50 subunit consists of 433 amino acids, and the p50 also has the RHD, within this domain there is an nuclear localization signal sequence (nuclear localization sequence), which is responsible for the translocation of dimers into the cell nucleus [21, 28, 29], contains information about nuclear localization and the glycine-rich region, which is considered to be a stop signal for the proteosome when processing p105 into p50. Also, ankiryn repeat domains are present in the protein, as well as one protein death domain (death domain) (Fig. 1) [5, 21].

Because of the differences in the C-terminal region of the peptide chain, 2 groups were distinguished among the NF-kB proteins. The first includes the proteins RelA, RelB and c-Rel, which contain the transcription activation domain sequence at the C-terminus, thanks to which they can activate the transcription of the DNA molecule. The second group consists of NF-kB1 (p105/p50) and NF-kB2 (p100/p52) proteins synthesized as p105 and p100 precursor proteins (105 and 100 kDa, respectively), which have an ARD domain (ankyrin repeat) in C-end domain containing several (5–7) ankyrin repeats [29, 30]. These repeats are responsible for the binding of NF-kB proteins to the

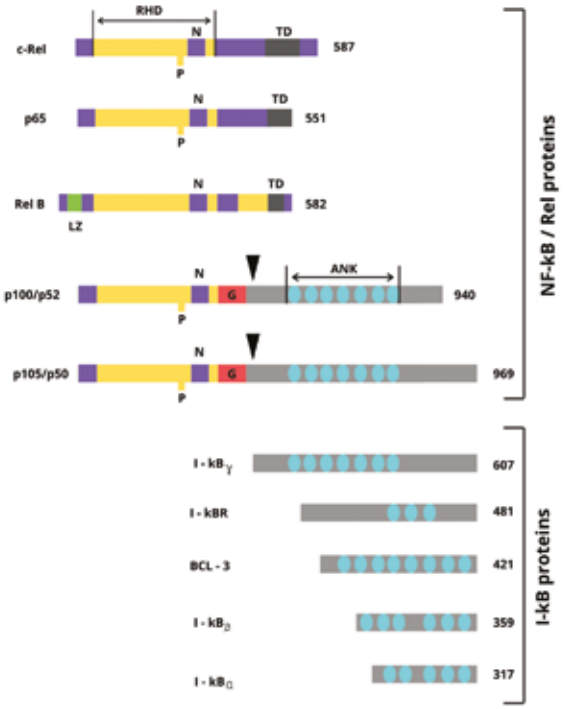

Fig. 1. Members of the mammalian Rel/NF-kB and IkB families of proteins

Note: The number of amino acids in each protein is shown on the right. The arrows point to the endoproteolytic cleavage sites of p52/p100 and p50/p100. ANK — ankyrin repeats; G — glycine-rich region; LZ — leucine-zipper domain of RelB; N — nuclear localization sequence; P — PKA phosphorylation motif; TD — transactivation domain

nuclear localization signal sequence. As a result of the ubiquitin-dependent proteolysis of these fragments, the final forms (p50 and p52) are formed, which have an RHD, due to which they can bind to a DNA molecule. However, they lack the transcription activation domain responsible for the activation of transcription, and therefore they function as repressors of transcription [31]. In addition, the p105 and p100 proteins have a glycine-rich region that prevents the complete degradation of these molecules in the proteasome. They also have an signal-sensitive region region in which the phosphorylation site of kB kinase inhibitor (IKK) is located [21].

Since the mechanism for the formation of the p105 precursor in the cell is much more efficient than the mechanism for the formation of the p100 precursor, most cells are characterized by high levels of the p50 protein, and the amount of the p52 protein is relatively small and tightly regulated [21].

NF-κB1 products are inactive in the cytoplasm and are bound with regulatory proteins called kB (IkB) inhibitors, of which IkBα, IkBβ and IkBε are considered the most important [32].

There are two main ways to activate *NF-kB1*.

The classical (canonical) pathway (Fig. 2, A) is the result of cellular exposure to cytokines, such as tumor necrosis factor α and interleukin-1, CD40 ligand, lymphotoxin β, or in response to inflammatory signals, such as bacterial lipopolysaccharide. These stimuli lead to a cascade of biochemical reactions

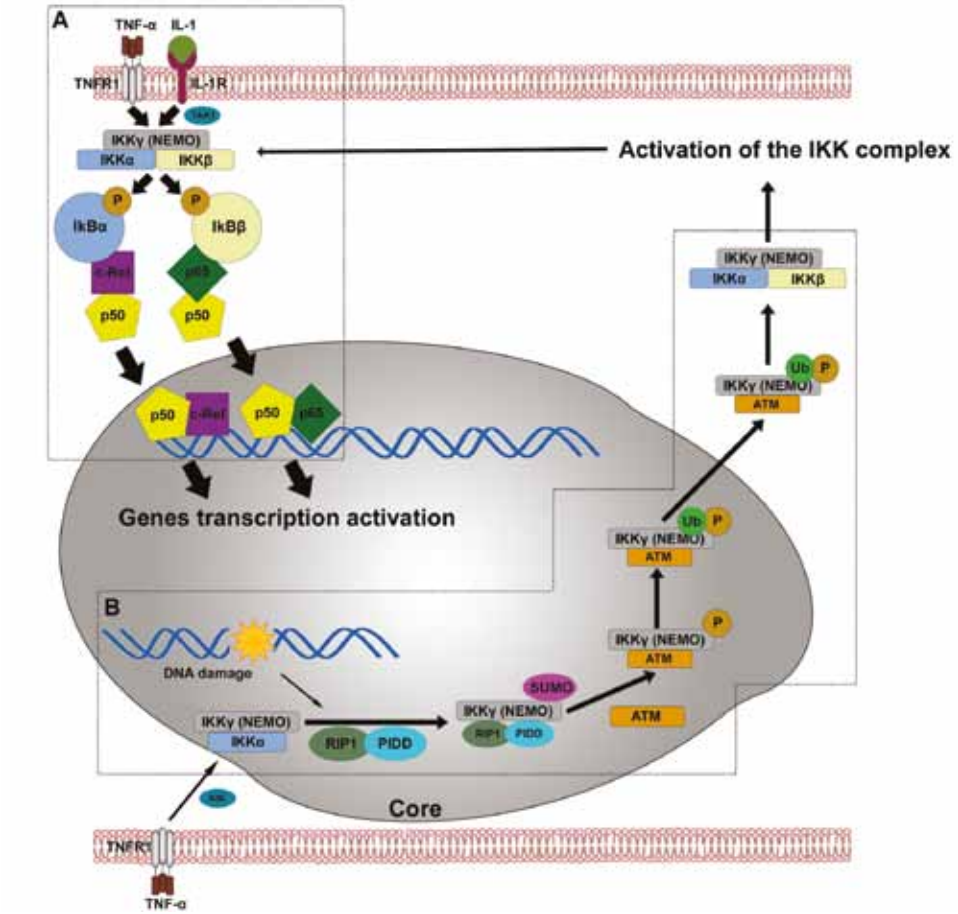

Fig. 2. Activation pathways of *NF-kB1*. A — the canonical pathway; B — non-canonical (atypical) activation pathway
Note: IL-1 — interleukin-1; SUMO — small ubiquitin-like modifier; TNFα — tumor necrosis factor α

that, through phosphorylation, activate IKK complex inhibitor consisting of IKKα (IKK1), IKKβ (IKK2) and the NF-kB essential modifier (NEMO, also known as IKKγ). When activated by kinase signals, IKK phosphorylates two serine residues located in the IkB regulatory domain. After phosphorylation of serines, the IkB inhibitor molecules ubiquitinate and undergo proteosome degradation [5, 33, 34]. After IkB degradation, the NF-kB complex, consisting of p50 and c-Rel or p50 and p65 enters the nucleus, where it can "enable" the expression of several genes that have binding sites for them [34, 35]. Activation of these NF-kB-regulated genes leads to a given physiological response (inflammation, immune response, cell survival, or cell proliferation). In addition, NF-kB turns on the expression of its own repressor IkBa, and the newly synthesized IkBa re-inhibits NF-kB, which forms a negative feedback loop. In some cases, this can lead to fluctuations in the level of activity of NF-kB [35].

The canonical nuclear NF-kappa B pathway is triggered by the signals from a large variety of immune receptors, which activate the TGFβ-activated kinase 1 (Fig. 2, A). TGFβ-activated kinase 1 then activates a trimeric IKK complex, composed of catalytic (IKKα and IKKβ) and regulatory (IKKγ) subunits, via phosphorylation of IKKβ. Upon stimulation, the IKK complex, largely through IKKβ, phosphorylates members of the inhibitor of κB (IκB) family, such as the prototypical IκB member IκBα and the IκB-like molecule p105, which sequester NFκB members in the cytoplasm. IκBα associates with dimers of p50 and members of the Rel family (RelA or c Rel), whereas p105 associates with p50 or REL (RelA or c-Rel). Upon phosphorylation by IKK, IκBα and p105 are targeted for ubiquitin-dependent degradation in the proteasome, resulting in the nuclear translocation of canonical NF-kappa B family members, which bind to specific DNA elements, termed kB enhancers of target genes, in the form of various dimeric complexes, including RelA/p50, c Rel/p50, and p50/p50.

Non-canonical (atypical) activation pathway. This pathway is activated when cell is exposed to various factors, in particular, when DNA is damaged due to chemotherapy, and radiation therapy, or it is triggered by NF-kB-inducing kinase (Fig. 2, B). DNA damage can induce alternative phosphorylation of the IκBα complex via casein kinase II and tyrosine kinases, which then canonically induce transcription of the *NF-kB1* gene [5]. In response to DNA damage, the NEMO subunit binds to the small ubiquitin-like modifier complex due to protein inhibitor of activated STAT ligase, then the NEMO — p53-inducible death domain-containing protein (PIDD) — receptor interacting protein 1 (RIP1) complex is formed and it undergoes phosphorylation of ataxia telangiectasia-mutated kinase activated by DNA damage. This process is fol-

lowed by ubiquitination of NEMO — PIDD — RIP1 that does not lead to the destruction of the complex, but allows it to translocate to the cytoplasm, where it activates the IKK complex [36]. Further, the process is identical to the classical activation pathway.

Thus, the classical and non-canonical pathways of NF-kB1 differ only in the way IKK activation, in the first case it is activated by inflammatory cytokines, and in the second by DNA damage. Given the role of inflammation in the development and progression of the tumor, NF-kB1 by default should play an important role in carcinogenesis. In addition, the genomic instability of the tumor, the effects of chemotherapeutic agents and radiation therapy creates a substrate for activation of NF-kB1 trough a noncanonical pathway, which can determine its value for the formation of chemo- and radioresistance and affect the outcome of the disease.

CLINICAL ROLE OF *NF-KB1*

It is known that *NF-kB1* plays an important role in tumor progression, metastasis, as well as the development of chemoresistance in patients with BC. As far back as 1998, Lin *et al*. [37] showed that *NF-kB1* activation occurs under the influence of a wide range of signaling molecules, and the product of this gene regulates the synthesis of dozens of proteins and factors responsible for many physiological processes in the body, by binding to promoters of target genes. Its main purpose is to switch cells from one development program to another in order to preserve the function of the organ and the whole organism.

In malignant tumors, in particular in BC and OC, there is a significant increase in the content of NF-kB1 protein in tumor cells. Guo *et al*. [11] found that the increased content of this product in the tumor is associated with the clinical stage of the disease and a high degree of malignancy. In another study, the authors showed that the expression of *NF-kB1* was dependent on the histological subtype of the tumor and correlated with the degree of malignancy and was associated with OC risk [38]. In addition, the launch of the atypical activation pathway of *NF-κB1*, through the action of ionizing radiation on the tumor cell, leads to a decrease in the radiosensitivity of cells [39, 40]. A similar result was shown for head and neck tumors [41].

As mentioned above, in case of DNA damage in tumor cells, one of the main ways of its restoration is the homologous recombination process, which is crucial for the efficient repair of double-stranded DNA breaks, and at the same time it is a marker of sensitivity of BC to chemotherapy [42]. HRD leads to genomic instability, in particular various chromosome aberrations [43]. Mutations in the *BRCA1* and *BRCA2* genes are one of the most well-known causes of HRD, therefore, the presence of germline mutations in these genes determines the high sensitivity of tumors to DNA-damaging agents [44]. It is important to note that even though there is a BRCA deficiency, alternative DNA repair pathways may be involved in tumors [45]. The most famous is the activation of the *PARP1* gene [15]. A group of scientists led by Sydney Shall in 1980 showed that the use of *PARP1* inhibitors may have an additional cytotoxic effect of alkylating agents on tumor cells [46]. Clinical studies have shown that *BRCA*-deficient tumors are sensitive to *PARP1* inhibitors and platinum agents [46]. Therefore, at the moment, treatment of *BRCA1*-associated OC is carried out using *PARP1* inhibitors. Recently, it was found that the activation of *NF-kB1* in response to DNA damage may be partially responsible for the chemoresistance and progression of BC, and overexpression of this gene may be associated with tumor metastasis [16, 47], which makes *NF-kB1* a promising marker in cancer patients, in particular, it is suggested that in patients with OC, activation of *NF-kB1* can lead to resistance to platinum preparations. A recent *in vitro* study showed that in the absence of the functional *BRCA1* gene, *NF-kB1* activity increases due to an increase in the level of reactive oxygen species.

In contrary, some authors suggest that the increased *NF-kB1* signalling contributes to the formation of an antitumor microenvironment and this determines the best outcome of the disease [48]. In one of the latest studies of BC patients, it was found that the transcription factor *NF-kB1* has prognostic value in triple-negative BC. Moreover, its higher expression is associated with high metastatic-free survival rates (HR 0.48, 95% CI 0.34–0.67, $p < 0.0001$) [49]. On the other hand, there are studies of triple-negative BC that show that overexpression of the *NF-kB1* gene, as well as 10 more genes included in this pathway, is associated with a low level of disease-free survival compared to a group of patients with low expression of *NF-kB1* ($p = 0.001$) [50]. In BC patients, it was shown that a high level of expression of nuclear RelA promotes activation of the canonical pathway of NF-kB and is associated with a poor prognosis [51]. Very often, the p65 and p50 subunits are active and overexpressed in BC, which leads to further transcription of genes such as *Bcl-x L, cIAP1, cIAP2* and *cFLIP* [52, 53]. Some authors, who conduct studies *in vitro* on the MCF-7 cell line have shown that targeted inhibition of the *NF-kB1* gene leads to a decrease in the activity of the NF-kB protein, which suppresses tumorigenesis [54]. Increased expression of *NF-kB1* in luminal BC is associated with resistance to hormonal therapy and is associated with low rates of non-metastatic survival [55, 56].

There are also studies on other localizations of malignant tumors. In the presence of inactivating NF-kB1 genotype del/del polymorphism rs28362491, a high degree of pathomorphosis is observed in patients with rectal cancer after chemoradiation therapy (OR 6.39; 95% CI, 0.78–52.65; $p = 0.03$). Also, patients with this genotype showed an increase in relapse-free ($p = 0.09$) and overall survival ($p = 0.04$) [57]. *NF-kB1* 94ins/delATTG polymorphism in multiple myeloma has also been associated with progression-free survival. The presence of delATTG determined lower survival rates ($p = 0.013$) [58]. The

level of *NF-kB1* gene expression is important in the progression of gastric cancer, as it has been found to be associated with tumor size, lymphogenous metastasis, and survival [9, 10]. Meylan *et al*. [59] showed that inhibition of the *NF-kB1* pathway leads to a significant decrease in tumor growth and concluded that signaling in the *NF-kB1* pathway plays a critical role in lung cancer carcinogenesis. In a study in patients with cancer of the oral mucosa, it was found that the level of *NF-kB1* mRNA in the tumor tissue is 3 times higher ($p < 0.05$) compared to the healthy tissue sample. In addition, a high level of expression of this gene was observed during lymphogenous metastasis ($p = 0.0001$). Interesting results have been demonstrated in kidney cancer. An objective response to treatment with targeted therapy with everolimus in patients with disseminated kidney cancer is associated with an initially high level of expression of *NF-kB1* [60].

Thus, for many malignant neoplasms, increased expression of NF-kB1 plays a negative role and is associated with low survival rates and the formation of chemo/radiation resistance.

INHIBITORS OF *NF-KB1*

It has now been shown that many chemotherapeutics and targeted drugs can alter the expression of *NF-kB1*, thereby affecting tumor progression. It was originally reported that taxanes inhibited the activity of *NF-kB1*, therefore inhibiting the formation of metastases [61, 62]. In contrast, doxorubicin, as well as anthracycline drugs, do not have sufficient activity to block the activation of this transcription factor [63]. It is important to note that despite the fact that doxorubicin inhibits the synthesis of DNA and RNA, as well as the enzyme DNA topoisomerase II, thereby blocking the transcription and replication of nucleic acids, DNA damage caused by doxorubicin activates the *NF-kB1* pathway, leading to the resistance of tumor cells (mainly in BC) to this anticancer agent [50, 64, 65]. In this regard, the synergistic effect of doxorubicin and taxanes with the use of doxorubicin/docetaxel) and doxorubicin/cyclophosphamide/docetaxel regimens becomes clear. Taxanes inhibit doxorubicin-mediated activation of *NF-kB1*, thereby enhancing the antitumor activity of the drugs.

Other drugs are also able to inhibit *NF-kB1*. These include the anti-inflammatory drugs specifically indomethacin, dexamethasone, salindac, tamoxifen [66]. This, in particular, is associated with the well-known antimetastatic effect of anti-inflammatory drugs in cancer patients.

Currently, in clinical practice of treatment of multiple myeloma, an indirect inhibitor of *NF-kB1* is used — bortezomib [67], which is primarily an inhibitor of the 26S proteosome. This drug is involved in inhibiting the proliferation and/or stimulation of apoptosis in various types of cancer, such as breast, gastric, ovarian, pancreatic tumors, etc. [7]. Bortezomib inhibits the activity of the *Sp1* gene and disrupts the interaction of the Sp1/RelA complex, which ultimately inhibits the *NF-kB1* pathway [68]. Some authors have shown that bortezomib can be a promising drug for the treatment of patients with tumors that are resistant to anthracycline-containing regimens. In such patients, in the presence of the active gene *NF-kB1*, a moderate antitumor effect is observed [69], the use of bortezamib will block the activity of *NF-kB1* and reduce resistance to doxorubicin. On the other hand, it also makes sense to try combinations of doxorubicin with anti-inflammatory drugs.

CONCLUSION

To sum up, *NF-kB1* is a very promising marker for the prognosis and formation of resistance to therapy, and can also be used as a marker for the development of targeted drugs. This gene is activated in response to DNA damage under the influence of chemo- and radiation therapy. Given the fact that *NF-kB1* is an activator of the transcription of many genes involved in carcinogenesis, tumor development and progression, the development of specific inhibitors will effectively complement chemo-, targeted or radiation therapy in a wide range of oncological nosologies. Studying the relationship of expression, loss of heterozygosity, chromosomal aberrations, etc. of the *NF-kB1* gene also seems to be interesting within the framework of the possible use of these parameters as predictive and prognostic criteria for prescribing treatment.

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CONFLICTS OF INTERESTS

Authors declare lack of the possible conflicts of interests

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