ASPECTS OF NF-kB TRANSCRIPTION FACTOR INVOLVEMENT IN SKIN PATHOLOGY

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Summary

The transcription factor NF-kB represents a protein structure that stabilizes the link between RNA polymerase and the promoter of the gene to be transcribed. NF-kB represents one of the most important transcription factors, indispensable for the transcription of a target gene.

The activation of transcription factors is evidenced by the products of genes to which NF-kB contributed to the transcription. In the case of NF-kB, they are products that stimulate inflammation (cytokines, chemokines, growth factors) or products that stimulate tumor proliferation by inhibiting apoptosis.

In pathological conditions, overactivation of NF-kB increases the transcription of genes encoding pro-inflammatory cytokines, forming the initiation and maintenance of inflammation. In tumor proliferation, NF-kB has an antiapoptotic action but also promotes metastasis, tumor vascularization, protumoral modifi-cations in the tumor mechanism. At the skin level, NF-kB is overexpressed in keratinocytes, immune cells, fibroblasts (atopic dermatitis) having an important role in the inflammatory processes that define these conditions. In the case of malignant melanoma, NF-kB is involved in the transcription of antiapoptotic genes favoring the survival of tumor cells. NF-kB also intervenes in the activity of the immune response checkpoints PD1 and CTLA-4.

Due to the major involvement of NF-kB in the pathology of these conditions, the possibility opens for NF-kB to become an important therapeutic target.

We present a series of aspects of the physiology and pathology of NF-kB with involvement in psoriasis, atopic dermatitis, malignant melanoma.

Keywords: *NF-kB, psoriasis, atopic dermatitis, malignant melanoma.*

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Gene expression (genetics) represents the process of transmitting hereditary information encoded by nuclear DNA to ribosomes where protein synthesis is carried out. It is a complex process that includes three stages: transcription, translation and the formation and functionality of the resulting proteins.

Transcription, the first stage of genetic expression involves copying genetic information from nuclear DNA grouped into genes (written in the nucleotide sequence) into a messenger RNA molecule. This will leave the nucleus, reach the cytosol and subsequently to the ribosomes where it will be decoded and protein synthesis will be carried out based on the genetic information transmitted from the nucleus.

The formation of mRNA is carried out by an enzyme called RNA polymerase, which forms a DNA chain identical to a DNA template chain from separate nucleotides, transferring the genetic information written in the nucleotide sequence into the newly formed DNA chain. For

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this process to occur, RNA polymerase must bind to protein structures called transcription factors and attach to a portion of the gene called the promoter. This is a sequence of 100-1000 base pairs, specific to each gene, where transcription must begin [1,2].

Transcription factors are essential proteins found in all eukaryotic cells, starting with sea anemones, that stabilize the RNA polymerase/ DNA complex and are also transcription regulators. There are many transcription factors, many of which act on the promoters of multiple genes [3].

In human pathology, the best-known transcription factor is the nuclear factor in B lymphocytes, which binds to the kappa enhancer of the gene encoding the kappa light chain of immunoglobulins, abbreviated NF-kB. The name reflects its discovery in B lymphocytes and the insertion site of the target gene.

HISTORY. NF-kB was discovered in 1986 by Ranjan Sen and David Baltimore, who identified a protein structure in B lymphocytes that binds to the promoter of the gene encoding the light chain of immunoglobulins. This factor was later named NF-kB. In the following period, the importance of the factor in initiating transcription of the gene encoding the kappa chain but also in the transcription of other genes was discovered [4].

The understanding of the activity of NF-kB in the transcription of numerous genes was completed by A. Potorak and B. Lamaitre who established that the TLR receptor (Toll like receptor) is an important pathway for activating NF-kB. Subsequently, numerous agents that can activate NF-kB were discovered [5].

STRUCTURE. In mammals, NF-kB is formed by 5 proteins: NF-kB1 (p105 which by cleavage becomes p50), NF-kB2 (p100, by cleavage becomes p52) and the proteins p65 (RELA), RELB, c-REL. RELA or homolog A of the viral oncogene of avian viral reticuloendotheliosis is encoded by the RELA gene which is involved in the modulation of the immune response and tumor proliferation.

Each member of this family contains at the N-terminal end a domain called RHD (REL Homology Domain) through which it couples with the other members forming dimers that can couple with specific regions of DNA but also with the regulatory proteins ikB. At the C-terminal end, the RELA, RELB, c-REL proteins present a TAD transcription domain that modulates dimerization and interaction with IKB [6,7].

NF-kB proteins are grouped into 2 classes based on the sequences at the C-terminal end. The first class is formed by the proteins p105/p50 and p100/p52 and the second group formed by RELA (p65), RELB and c-REL. The first group contains proteins that do not activate transcription but become active by dimerization with proteins in the second group. This forms dimers with the first group and binds to the ikB site on DNA, having a major role in the activity of RNA polymerase [7,8]. All of these proteins form dimers but not all dimers have transcriptional activity, the p-50 RELA dimer being the most active. In current language the term NF-kB refers to the p50-RELA dimer [8].

IkB proteins. The IkB protein family comprises three members IkBα, IkBβ and IkBγ. These members share a domain that can be phosphorylated by IKK kinases. IkB proteins, by dimerizing at the RHD domain level with REL dimers of NF-kB, cover the binding sequence of these domains at the nuclear DNA level, becoming inactive and remaining in the cytosol. NF-kB inhibition can be achieved to a lesser extent by p100 and p105 when they do not form dimers with REL family members [7,9].

IKK kinases. The release of NF-kB dimers from the complex with IkB is done by the activation of IKK kinases. They form a three-member family, two kinases IKKα and IKKβ and a subunit IKKγ (NEMO) with a regulatory function. IKB inhibitory proteins bound to NF-kB dimers are phosphorylated and degraded by IKK kinases. The release of NF-kB dimers allows them to migrate into the nucleus and attach to the KB site, initiating transcription. Various cellular stimuli can induce the activation of IKK kinases releasing NF-kB dimers but also the inactivation of IKK through autophosphorylation [8,9,10].

ACTIVATION OF NF-KB. NF-kB is found inactive in the cytosol bound to IkB proteins. The action of IKK kinases releases NF-kB which can enter the nucleus mediating the activity of RNA polymerase. Activation of NF-kB involves the

activation of IKK kinases which degrade IkB. Numerous extracellular and cellular stimuli can activate IKK enzymes through biochemical cascades, true NF-kB activation pathways. Two NF-kB activation pathways have been identified so far: the canonical and noncanonical pathways, each with a certain specificity.

Depending on the molecules participating in the activation of IKK enzymes (receptors, ligands, adaptor molecules, enzymes) but also on the biological processes that are initiated by the transcription of target genes [11].

Canonical pathway. It represents the main pathway for NF-kB activation, involved especially in the inflammatory response to pathogens, especially microbes, by stimulating the transcription of genes encoding proinflammatory products (cytokines, chemokines) but also of other processes [12].

Canonical pathway is activated by a series of stimuli such as: antigen receptors (BCR, TCR), TLR (toll like receptor) TNFR, IL-1, antigens, LPS, growth factors, cytokines, bacterial and viral products, reactive oxygen species, stress [8,13].

Depending on the nature of the stimuli, an enzymatic cascade is activated that ultimately acts on NEMO which, through a specific domain, attaches to IKK enzymes. Oligomerization of the NEMO subunit, which contains a specific IKK activation domain, and phosphorylation of IKKα and IKKβ, and release of NF-kB dimers from the complex with IkB occur, which can migrate into the nucleus. In the case of activation by antigen through BCR or TCR, NEMO is reached through an enzymatic chain different from TNFα or IL-1β, forming the CARMA1/ BCL10/ MALT1 complex and finally NEMO activation [8].

There are multiple pathways for regulating NF-kB activation, the most important being through the A20 protease which under certain conditions in the cytosol can destabilize the IKK complex [12]. The canonical pathway has a rapid but transient action, its activation being largely dependent on the nature of the stimulus [13].

The noncanonical or alternative pathway. It is activated by lymphotoxin, BAFF (lymphocyte activation factor) RANK (NF-kB receptor activator), the CD40 ligand. Activation via this pathway does not require activation of IKKβ or NEMO. This pathway also involves the activation and processing of p100 which can be cleaved resulting in p52 which can couple to REL proteins.

The main element of this pathway is represented by the NIK kinase - an inducing kinase of NF-kB and IKKα. NIK phosphorylates IKKα which in turn contributes to the phosphorylation of p100 which is cleaved and p52 is formed. P52 forms dimers with REL proteins resulting in active forms of NF-kB. An important element of this pathway is the TRAF system (TNF receptor associated factor/cIAP) which maintains NIK at basal levels [11,12]. Recruitment and activation of TRAF2 and TRAF3 activate the non-canonical pathway while activation of TRAF6 is present in the canonical pathway [8,13].

The relationship that is established between the two NF-kB activation pathways can be diverse, synergistic, independent or competitive. At the same time, NF-kB activation and implicitly the activation of gene transcription interact in different ways with other biochemical signal transmission pathways such as: MAPK, JAK-STAT, TGFβ, WNT, NOTCH, HEDGEHOG [8,14,15].

NF-kB IN PATHOLOGICAL PROCESSES. The NF-kB signaling pathway represents one of the most important signaling pathways at the cellular level. The final result of NF-kB activation consists in the action of the final products (cytokines, chemokines, growth factors, ligands) of the transcribed genes. NF-kB can interact with a multitude of genes. The genes encoding the components of the NF-kB pathway present numerous mutations that are found in the functionality of NF-kB either through loss of function or gain of function [16]. Mutations in NEMO have frequently been associated with skin inflammation, hair, nail, and tooth abnormalities, or with the IKKα and IKKβ enzymes, the IKB inhibitory complex, or REL proteins [8]. The transcription of numerous genes in which NF-kB is involved causes NF-kB to participate in biological processes under normal conditions, such as: cell survival and proliferation, metabolism and homeostasis, and rapid adaptation to environmental changes [7,8]. The most important

and best documented pathological processes in which NF-kB is involved are inflammation/ immune response and tumor proliferation.

NF-kB in inflammation. Inflammation is a complex response of the body triggered by microbial agents, foreign bodies, and various agents from the internal or external environment. Through the inflammatory response, the body seeks to destroy or limit the action of pathogens and restore damaged structures and functions. The inflammatory response is initiated and coordinated through several signaling pathways.

Activation of NF-kB increases the production of proinflammatory cytokines in lesional somatic cells but also in the innate and adaptive immune system. Vascular, cellular and humoral changes occur that occur in the inflammatory focus but also in immune cells resident or recruited to the inflammatory focus [17].

The canonical pathway is the main pro-inflammatory pathway for NF-kB activation. It is initiated by the action of various stimuli: cytokines (TNFα. IL-1β) B and T receptors on lymphocytes, TLR (toll like receptor) by recognizing PAMP structures (on the surface of the pathogen) and DAMP (cell damage products). Activation of IKK enzymes is a central point in the activation of NF-kB [8]. Activation of NF-kB induces the assembly and initiation of the action of inflammasomes, protein structures that through caspases activate proinflammatory cytokines but can also have a destructive action generating a form of cell death through apoptosis.

Activation of the NLRP3 inflammasome by NF-kB is also associated with the inhibition of NF-kB action, preventing excessive inflammation through negative feedback [18].

The p50 monodimer can produce a decrease in NF-kB activity. NF-kB has a dual action in the case of apoptosis. In most processes, including inflammation, NF-kB acts as an antiapoptotic factor, promoting the survival of immune and non-immune cells, by acting on anti-apoptotic genes.

But NF-kB can also have a proapoptotic role by promoting the transcription of proapoptotic genes or by mediating the degradation of p53 gene products [8, 19].

NF-kB in the immune response. NF-kB is involved in both innate and adaptive immunity.

The main cells of innate immunity, macrophages and neutrophils, are involved in the inflammatory response.

Macrophages are activated by the recognition of PAMPs and DAMPs, as well as other receptors such as NOD, RIG, GMP-AMP. All of these receptors activate NF-kB and other signaling pathways. By activating NF-kB, macrophages switch to the M1 inflammatory phenotype with the massive production of proinflammatory cytokines (IL-1, IL-6, TNF). Under certain conditions, macrophages switch to the M2 phenotype with the production of cytokines that inhibit inflammation. The NF-kB pathway also promotes the phagocytosis of pathogens by macrophages [7,20,21].

In response to TLR stimulation through the adaptor protein TRIF or MYD88, the canonical NF-kB pathway is activated with the massive production of IFNα and IFNβ [21].

Neutrophils. NF-kB acts as a regulator of proinflammatory gene expression and increases the expression of anti-apoptotic genes, prolonging the duration of activated neutrophil activity. It has been observed that non-activated neutrophils contain more Ikbα, an inhibitor of NF-kB. Stimulation via the TLR pathway induces IkBα degradation. In granulopoiesis, NF-kB is proapoptotic, suggesting a dual effect of NF-kB action in neutrophils [21,22].

Langerhans cells. They are the main antigen-presenting cells in the immune response. They are stimulated via the canonical pathway and transform into mature antigen-presenting cells. They are also stimulated via the alternative pathway by TNF, CD40, RANK. The development of Langerhans cells is increased by RELB, while the increase in NF-kB activity in Langerhans cells is dependent on TLR2 and TLR4 [7,22].

In adaptive immunity, NF-kB activation is absolutely necessary for the development and functionality of T and B lymphocytes. In the case of T lymphocytes, NF-kB is absolutely necessary for antiapoptotic and lymphopoietic function [21]. The coupling of the antigen receptor with MHC peptides induces NF-kB activation with a final proinflammatory and immunoregulatory response. In this case, activation occurs via the canonical pathway. The noncanonical pathway

plays a role in the development of Tγδ and NK cells. NF-kB activation through the medium of transcribed cytokines induces the differentiation of T lymphocytes with the CD4+ form [21,23]. The generation of Th1/Th2 polarization with a predominance of Th1 requires the mediation of c-REL. NF-kB also regulates the differentiation of Th17 cells. RELA deficiency in antigen-presenting cells reduces the production of cytokines that regulate differentiation into Th17 [20].

NF-kB is involved through the canonical pathway in the production and activation of Treg lymphocytes with an essential role in autoimmunity. And the alteration of NIK in the noncanonical pathway leads to a decrease in the number of Treg lymphocytes. NF-kB represents an essential signaling pathway for the activation of T lymphocytes or under some conditions can induce proapoptotic signals [24].

B lymphocytes. In the case of T lymphocytes, NF-kB is absolutely necessary for the development and activity of B lymphocytes. The coupling of the B receptor for antigen with antigen produces the activation of NF-kB and increased cytokine secretion. The activation pathway is both canonical and noncanonical. Blocking RELA and c-REL induces a block in the development of B lymphocytes. This is also done by the depletion of p50 and p52 monodimers. Also, the development of Ikkα and Ikkβ or NEMO decreases the number of mature B lymphocytes [7,25].

Autoimmunity. Activation of NF-kB in T cells can also be mediated by autoantigens. Activation via the canonical pathway plays a central role in T cell activation, including when coupled with autoantigens. The noncanonical pathway also plays an important role.

Overexpression of NIK induces autoimmunity. NF-kB has a role in stimulating autoimmunity but also in suppressing it by modulating the suppressive functions of Treg lymphocytes.

NF-kB is also involved in the establishment and maintenance of immune tolerance. Its action at the thymic epithelium (mTEC) level during T cell selection and inactivation of autoreactive T lymphocytes is particularly important. It is possible that both the canonical and noncanonical pathways are involved in the activation of thymic epithelial cells, favoring cells involved in the activation of cells involved in the negative selection of autoreactive T lymphocytes [20,27].

Tumor proliferation. This process involves uncontrolled cell growth with invasion of adjacent or distant tissues, with alteration of proliferation regulation mechanisms and signaling pathways including NF-kB.

NF-kB activity in tumor cells is similar to normal cells, but the target genes that are transcribed are mainly oncogenic.

NF-kB proliferative activity is present in excess in tumor cells, presenting an important but not major role in tumor development. At the same time, the NF-kB transcription pathway promotes vascularization, metastasis, or inhibits tumor cell apoptosis [28].

In most cancers, NF-kB activity is increased due to increased stimulation by TNFα and IL-1 but also to mutations that occur in oncogenes, genes that encode components of the NF-kB pathway [21]. NF-kB activation in solid tumors occurs mainly through the canonical pathway, while in hematological tumors it occurs through the noncanonical pathway [28]. Mutations in the genes encoding the REL and IκB proteins and the IKK enzymes have been detected [21]. Most mutations are gain-of-function, less frequently loss-of-function mutations activating IKKβ [21]. In murine models, knockdown of IKKβ has led to a significant decrease in tumor proliferation [29].

There are mutations that lead to the overexpression of components of the NF-kB pathway that are deregulated in different types of cancer. For example, RELA is overexpressed in ovarian cancer, c-REL in lung cancer [28].

It has been observed that in most cancers there is alteration of several signaling pathways that interfere with each other, including NF-kB [21,30].

In addition to the excessive proinflammatory action and mutations in NF-kB components, the protumor action of NF-kB is also manifested through a series of biological processes that favor tumor growth: angiogenesis, apoptosis, metastasis, immune evasion, metabolic reprogramming, resistance to therapy [21].

In apoptosis, NF-kB has a dual role, namely antiapoptotic promoting the survival of tumor cells but also proapoptotic to destroy them. The

ratio of pro- and antiapoptotic genes that are transcribed by NF-kB activation is important [8]. At the same time, the NF-kB pathway promotes the degradation of p53 gene products, which has the effect of increasing the number of cells with altered DNA and transmitting this altered DNA to daughter cells, favoring the occurrence of mutations [21,31].

The antiapoptotic action of NF-kB is achieved mainly by the transcription of antiapoptotic genes from the BCL-X family but also by the activation of IAP and FLIP proteins that inhibit the activation of caspases [32].

In the process of metastasis, NF-kB, through the transcription of EMT (epithelial mesenchymal transition) associated genes, mainly genes encoding transcription factors (TWIST, SNAIL, ZEB1), modulates intercellular adhesion molecules (integrins, selectins) and favors the appearance of the premetastatic niche. Through EMT, tumor cells acquire properties of mesenchymal cells with increased mobility, being able to migrate into various tissues [8,33,34,35].

NF-kB is active at the tumor microenvironment (TEM) level, favoring the suppression of cells with antitumor activity (macrophages, NK cells) surrounding the tumor and ultimately its progression.

By increasing cytokine production, activation of several signaling pathways, including NF-kB, phenotypic changes occur in cells in the tumor microenvironment (e.g. macrophages), which acquire immunosuppressive pro tumoral or antitumor properties [8,39].

Metabolic reprogramming is one of the pathways in which NF-kB is involved in order for cells to acquire immunosuppressive or protumor properties [36].

NF-kB is involved in resistance to various types of antitumor therapies: chemotherapy, radiotherapy, immunological therapy blocking immunological checkpoints.

Resistance to therapy is achieved by activating antiapoptotic genes, activating the NF-kB pathway, interfering with other signal transduction pathways (NOTCH, STING). Increased cytokine secretion leads to drug resistance by increasing the activity of pro-inflammatory cytokines (metabolic reprogramming)[8.37]. Although it is deeply involved in resistance to antitumor therapies, NF-kB has a dual role, sometimes accelerating the action of antitumor therapy. In murine models, it was observed that NF-kB inhibition reduced drug-induced apoptosis of tumor cells and some cytostatic induce apoptosis via the NF-kB pathway [38].

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NF-kB is an important pathway for transmitting transcription signals for numerous genes connecting external and internal stimuli with the transcription of proteins with various functions. At the same time, NF-kB activity is correlated with the action of other transcription pathways. All these products transcribed by NF-kB participate in numerous normal or pathological biological processes. The main processes in which NF-kB is involved are: inflammation, immune response and tumor proliferation. NF-kB activation is a main pathway for the production of proinflammatory cytokines (TNFα, IL-1, IL-6), chemokines (CXCL-1, CXCL-2) growth factors, essential elements in inflammation but also elements promoting tumor proliferation. Thus, persistent inflammation increases the risk of tumor proliferation [33].

Added to these is the action of NF-kB on the innate and adaptive immune response or the action on apoptosis. It can be said that NF-kB makes (Su explains) a connection between chronic inflammation and cancer. However, the action of NF-kB is dependent on the cytosolic context in which the cell is found at a given time.

CUTANEOUS DISEASES. At the skin level, NF-kB activation is highlighted both in inflammatory diseases (psoriasis) and in tumor proliferation (malignant melanoma). The specificity of each disease within the same process (example: psoriasis/atopic dermatitis) depends on a multitude of factors that are associated with the action of NF-kB.

NF-kB is a transcription factor majorly involved in inflammatory processes by activating the transcription of genes encoding proinflammatory cytokines. At the same time, NF-kB activation is carried out by a multitude of factors but also by proinflammatory cytokines creating an inflammatory loop that exacerbates inflammation at the lesional level.

As expected, the level of active NF-kB is increased in keratinocytes stimulating cytokine secretion and their proliferation. NF-kB also has increased values in Il-17-producing cells (Th17 in particular) and IL-23-producing cells [40].

Psoriasis. Psoriasis is an inflammatory, autoimmune skin condition in which there is a massive alteration of the cytokine network that affects cells involved in the immune response (T cells in particular), dendritic cells, keratinocytes.

NF-kB is activated in both pathways, with the canonical pathway being predominant, activated by internal and external factors, including cytokines, but also having numerous blocking systems. The canonical pathway includes p50/REL-A, p50/c-REL and is dependent on the functionality of the NEMO factor.

The noncanonical pathway is more selective in terms of activating factors, being independent of NEMO but dependent on NIC. The importance of the noncanonical pathway also results from the fact that it is activated by TNF, a cytokine with a strong inflammatory role in psoriasis by creating the TNF/IL-23/IL17 chain. However, the noncanonical pathway decreases the ability of dendritic cells to produce IL-23 and decreases the number of Th17 cells, which produce IL-17A, interrupting the inflammatory spiral produced by IL-17, limiting inflammation [41].

The involvement of NF-kB in the pathology of psoriasis is also evidenced by changes in genes encoding NF-kB components. An example is the gene encoding c-REL. Genetic changes in c-REL inhibit keratinocyte growth and decrease the production of Il-23 [8,42,43].

Another gene involved in the pathology of psoriasis related to NF-kB is the ACT1 gene (adaptor protein of IL-17 signaling). The ACT1 gene encodes a protein that activates NF-kB by acting on the kinase IKK, releasing NF-kB from the NF-kB/IkB complex. ACT1 also activates other signaling pathways but is strongly associated with the risk of developing psoriasis and psoriatic arthritis [44,45].

Genome-wide association studies (GWAS) have identified numerous single nucleotide polymorphisms (SNPs) at the general level encoding NF-kB component proteins. For example, the gene encoding p50 (SNP rs28362401 mutations) or the genes encoding IkBα (SNP 12883345 and SNP 7152376) [46]. An attempt has been made to establish a link between SNP mutations in genes encoding NF-kB components and response to TNF/IL23, IL-17 blocking therapies, but the results have not been conclusive.

Atopic dermatitis. It is an inflammatory skin condition with significant genetic determinants in which there is an exacerbation of Th2 lymphocytes.

NF-kB, which is heavily involved in proinflammatory processes of any type, is also involved in atopic dermatitis by promoting the transcription of genes encoding proinflammatory cytokines.

There is an increase in NF-kB activity in lesional keratinocytes, Th2 lymphocytes, but also in fibroblasts in the lesion. The decrease in NF-kB activity in these cells decreases cytokine production, decreases the recruitment of immune cells to the lesion, reducing inflammation overall. It has been shown that loss of IKKβ function in skin fibroblast cell cultures predisposes to skin inflammation and atopic dermatitis [John Seykora 2022]. Also, inhibitors of IKK kinases by degrading IkB and activating NF-kB may have significant clinical effects [47].

Although both atopic dermatitis and psoriasis are inflammatory conditions, there are differences in the activation of NF-kB. The HMGB1 (high mobility group protein1) -TLR-NF-kB pathway is active in atopic dermatitis and not in psoriasis [48].

In recent years, topical preparations with NF-kB activation blockers have appeared, but their use is not included in current clinical practice.

Malignant melanoma. Like most solid tumors, it shows increased NF-kB activation. Components of the NF-kB pathway (P50, REL-A) are overexpressed in tumor melanocytes compared to normal cells. It has been shown that REL-A is over phosphorylated, becomes active, and accumulates in tumor melanocytes and to a lesser extent in melanocytes from dysplastic nevi [49].

NF-kB activation in tumor melanocytes is dependent on increased IKK kinase activity, increased osteopontin expression, and BRAF mutations.

Osteopontin is a glycoprotein both intracellular and extracellular that is strongly as-

sociated with tumor proliferation through NF-kB activation [50,51].

BRAF gene mutations affect IkB stability by activating NF-kB, inducing resistance to apoptosis [50]. NF-kB is a signaling pathway that becomes hyperactive, leading to the transcription of proteins that deregulate the cell cycle, proliferation and cell survival.

The regulation of the cell cycle is done through cyclin D1, which controls the passage of cells from the G1 phase to the S phase. Overexpression of cyclin D1 causes the cell cycle, in the case of tumor melanocytes, to be accelerated and to no longer respond to antiproliferative control mechanisms, favoring tumor proliferation.

Activation of NF-kB increases the expression of cyclin D1, indirectly promoting tumor proliferation [50,52].

As in other types of cancer, NF-kB promotes antiapoptotic mechanisms and is a major element of apoptosis inhibition. Antiapoptotic genes from the BCL-2 family (BCL-XL), IAP genes or proteins such as TRAF1 and TRAF2 (tumor necrosis factor assumed factor 1 or 2) are activated. On the other hand, caspases, enzymes that destroy subcellular structures during apoptosis, can activate but also limit the action of NF-kB [50,55].

NF-kB is strongly involved in the activation of the immune response checkpoints PD1 and CTLA-4.

PD1 (programmed death protein) is a receptor on T and B lymphocytes. The coupling of PD1 with its ligand PDL-1 suppresses the action of T and B lymphocytes and the general immune response. Tumor cells that express PDL-1 ligands on their surface couple with the PD1 receptor on T lymphocytes, suppressing their antitumor response.

It has been shown that NF-kB increases the expression of PDL-1 on tumor cells, contributing to the decrease of the antitumor immune response with the appearance of the phenomenon of "escape" or avoidance of the antitumor response [54].

Another checkpoint of the immune response is CTLA-4, it is a receptor on the surface of activated T lymphocytes and regulatory T. Binding to specific ligands CD80 or CD86 (B7-1, B7-2) on antigen-presenting cells, but also on tumor cells, including tumor melanocytes, inhibits the antitumor activity of cytotoxic T lymphocytes as well as the general immune response. The relationship between CTLA-4 and NF-kB is particularly complex; the latter may contribute to the expression of CTLA-4 with the reduction of the antitumor response. CTLA-4 can inhibit several transcriptional pathways, including NF-kB, which can induce T-lymphocyte activation. It has been experimentally shown that inhibition of NF-kB activation can be dependent on CTLA-4 activation [55,56].

NF-kB is involved in numerous processes related to tumor proliferation in malignant melanoma, metastasis, autophagy, modeling of the tumor microenvironment, tumor and peritumoral vascularization without presenting special aspects found only or predominantly in tumor melanocytes.

NF-kB has a major role in the establishment of drug resistance found in malignant melanoma. There are several mechanisms by which it induces or participates in drug resistance: apoptosis and other types of cell death. Autophagy, activation of cellular pumps for the elimination of cytostatics from the tumor cell (via the MDR genes encoding the essential P-glycoprotein in this process) the action of PD1 and CTLA-4. Paradoxically, in certain circumstances, NF-kB activation is given by some cytostatics. To this are added the BRAF and N-RAS gene mutations that occur after anti-BRAF therapy in which there seems to be an indirect involvement of NF-kB through cytokines [51,58].

The major mechanism of induction of resistance to various antitumor drugs (chemotherapy, radiotherapy, immunological therapy) is represented by the blocking of tumor cell apoptosis through the transcription of antiapoptotic genes induced by several factors including NF-kB. Therapeutically, avoiding the blocking of apoptosis in tumor melanocytes is done by targeting several immunological checkpoints associated in the future with the limitation of NF-kB activity in these cells [59].

Conclusions

The transcription factor NF-kB represents a protein structure that stabilizes RNA polymerase at the promoter of the gene to be transcribed.

In the absence of the transcription factor, transcription cannot occur. Several transcription factors are known and each can be involved in the transcription of several genes. NF-kB activation is done by internal or extracellular stimuli that trigger a series of biochemical events in the cytosol (peptide cleavage, NF-kB assembly) its activation and entry into the nucleus.

Under physiological conditions, NF-kB signaling supports cell survival by ensuring an optimal cytokine flux, consistent with the stimuli the cell receives. The result of NF-kB activation is found in the action of transcribed products, cytokines, chemokines, growth factors, ligands, proteins involved in apoptosis.

In pathological conditions, excess NF-kB, in most cases, is involved in exacerbating or modulating the inflammatory process and the immune response. In the case of tumor proliferation, excess NF-kB favors the development of tumor cells, metastasis, tumor vascularization, protumor changes in the tumor microenvironment, blocking the immune response by acting on checkpoints.

In some cases, NF-kB can limit tumor progression. The transcription of antitumor genes is the major mechanism of NF-kB action in tumor proliferation, in some cases, NF-kB may also have an antitumor action.

At the cutaneous level, psoriasis and atopic dermatitis are inflammatory conditions in which NF-kB is strongly involved. Excess activation plays an important role in the pathogenesis of these conditions. Although in both cases it has a major proinflammatory role, the way in which this effect is achieved is not entirely identical.

In melanoma, overexpression of NF-kB favors tumor progression through mechanisms known to other solid tumors. Excessive activation of the immune response checkpoints PD1 and CTLA-4 is important in melanoma.

The knowledge gained about NF-kB opens new perspectives in therapeutics through the possibility of modulating the action of this transcription factor in two important processes of human pathology: inflammation and tumor proliferation.

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Conflict of interest
NONE DECLARED

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